Aerobic exercise and cognitive behavioral therapy in FSHD:
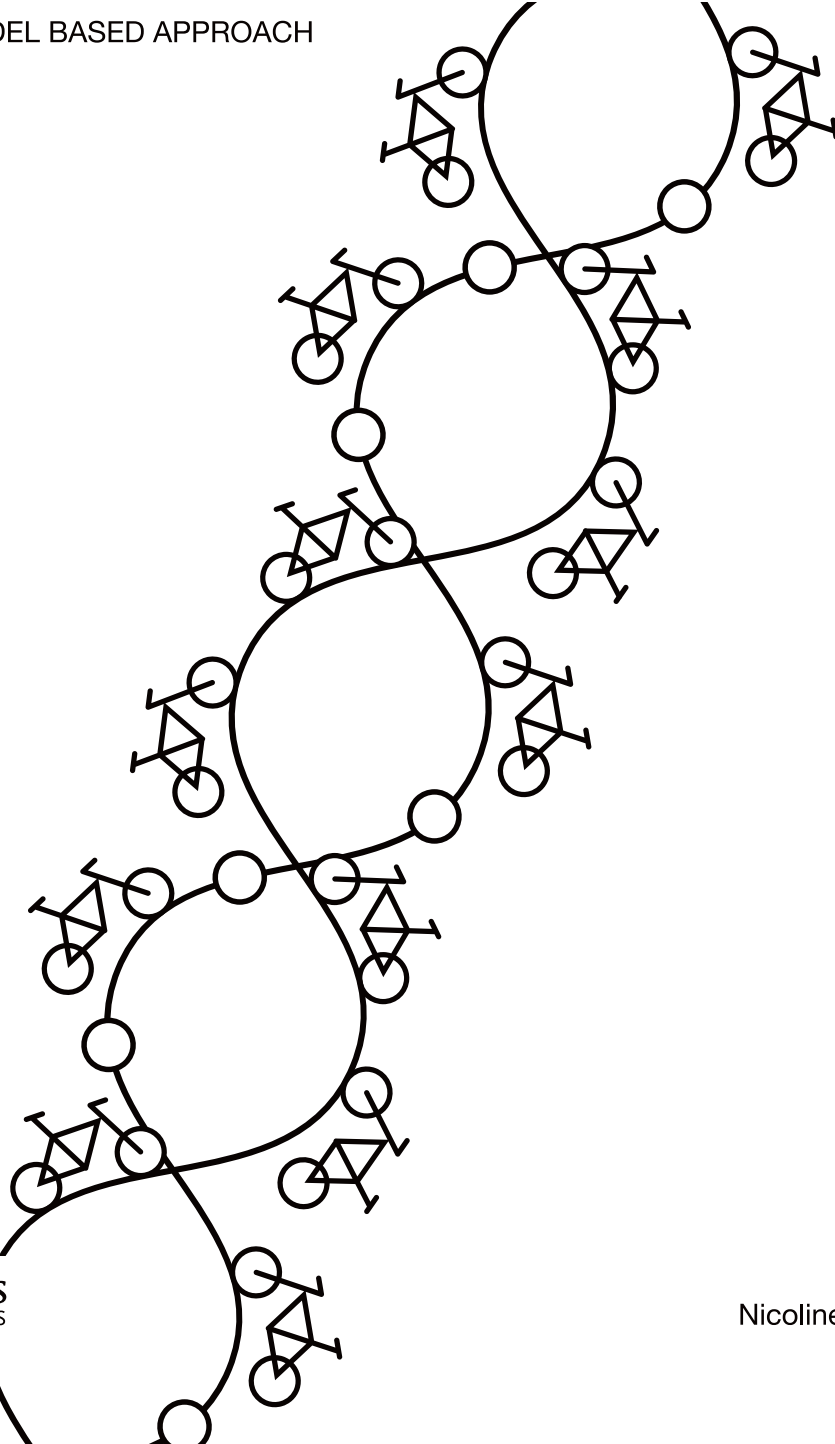
A MODEL BASED APPROACH

Nicoline B.M. Voet

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volgens besluit van het college van decanen
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door

Nicoline Berendina Maria Voet

geboren op 15 april 1983 te Nijmegen

CONTENTS

Voor papa en mama

CHAPTER 1

GENERAL INTRODUCTION

Mr. C is a 58-year old man with FSHD diagnosed at the age of 22. Apart from this muscle disease, he has always been healthy. He has worked fulltime most of his life but, since five years, he has been declared unfit for work. He used to live in a home with a garden, together with his wife. Because he was not able to walk stairs anymore, they were forced to move to an apartment with a small balcony. Since gardening was his hobby, he lost his main activity which he replaced by taking a nap every afternoon. At night, he is frequently awake and in the morning he is already fatigued from the beginning of the day. His wife wants him to go with her to family and friends, but he is reluctant to do so because he hates talking about his disease and getting all sorts of well meant advice. He is afraid that exercise might damage his muscles, as he regularly experiences muscle pain after physical activity. As a consequence, he has stopped his daily cycling sessions on a home trainer. His maximal walking distance has decreased to just a couple of hundred meters, which makes him increasingly home-bound. All together, his changing condition and circumstances have drawn him into a vicious circle of physical inactivity and fatigue, with a great impact on his quality of life.

For patients with facioscapulohumeral muscular dystrophy (FSHD), medical involvement often stops after receiving the diagnosis but, from their perspective, the need for medical attention has just begun. Patients, clinicians and researchers are searching for a curative treatment but, meanwhile, care for the consequences of the disease is just as important, especially in the short turn. Many patients with FSHD try to keep up their participation in social life and work. Citing a patient with FSHD: "You just want to live your life like everyone else. That should be the aim of medical research". Yet, being physically active is difficult for patients due to muscle weakness. The resulting reduction in aerobic capacity further restricts social participation. Moreover, more than 60% of the patients with FSHD are severely fatigued (1). In the past, fatigue in FSHD has received little attention as it was regarded as an untreatable problem patients "just had to live with". Consequently, patients did not often spontaneously complain of fatigue. Still, recognition of fatigue in FSHD is important for patients, whereas understanding and treating fatigue is a great challenge for researchers and clinicians. Fortunately, medical attention for fatigue is increasing.

FSHD

FSHD is the third-most common muscular dystrophy. The estimated prevalence is one in 8,000 persons (2). FSHD is an autosomal dominant disease. It is associated with subtelomeric contraction of the D4Z4 repeat region at chromosome 4q, with

loss of tandem repeat units and toxic expression of the DUX4 gene in muscle cells (3). In unaffected individuals, the D4Z4 array consists of 11 to 150 repeats, whereas FSHD patients have only 1 to 10 repeats. In general, the disorder is more severe in patients with lower numbers of repeats (Figure 1). Individuals genetically determined to have FSHD, however, show a wide range of clinical severity, age of onset, and rate of disease progression, including some who remain asymptomatic throughout their lives. This variability suggests that the disease has a strong epigenetic component.
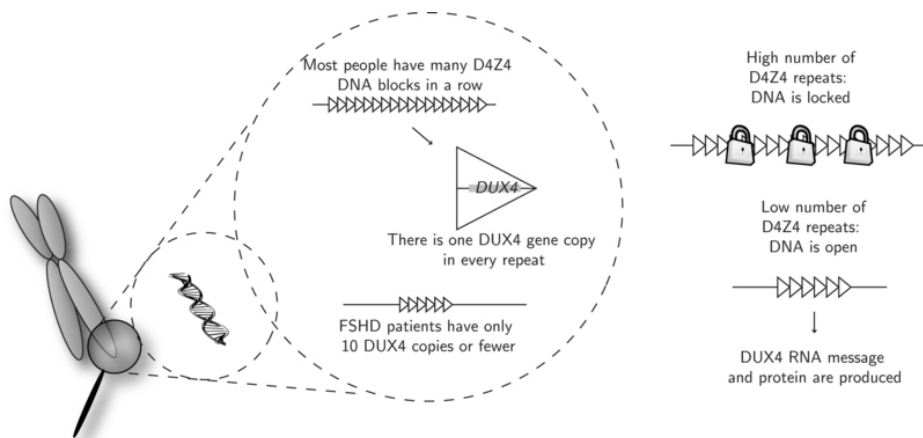
Figure 1 FSHD is linked to the 4qQ subtelomere and the epigenetic status of the 4q35 D4Z4 array

When D4Z4 is composed of many DUX4 copies the DNA becomes 'locked'. As a result, the DUX4 gene is switched off or 'silenced'. However, if there are only a few DUX4 copies, the DNA 'relaxes' and becomes accessible. When this happens, the DUX4 gene is switched on resulting in carbon copies of the gene being made – called RNA. These contain the instructions to build a DUX4 protein. Figure courtesy of Andreas Leidenroth (4).

Epigenetics concerns the mechanisms other than DNA sequence that influence gene expression. An example of an epigenetic mechanism is DNA methylation, a process by which methyl groups are added to DNA. The more methylation, the tighter the chromatin is compacted and the less the gene inside is expressed. Conversely, reduced methylation (hypomethylation) relaxes the chromatin and increases the likelihood of gene expression. Healthy individuals have numerous D4Z4 repeats which are highly methylated (Figure 1) (4). FSHD1-affected individuals have few repeats and these are hypomethylated. FSHD1 asymptomatic or unaffected individuals also have few repeats, but these have a higher degree of methylation (5). Recently, a new subtype of FSHD, type 2, (FSHD2) was identified (6). The symptoms of FSHD1 and FSHD2 are similar; the difference between

the conditions is their genetic locus and frequency of occurrence (7). FSHD2 individuals have many D4Z4 repeats, like healthy individuals, but they are severely hypomethylated (6).

FSHD2 is much less prevalent than FSHD1. Current research projects try to identify and manipulate the epigenetic regulators of the DUX4 gene expression in both FSHD1 and FSHD2 in order to decrease the symptoms of the disease.

FSHD derives its name from the muscle groups that are affected first: facial and shoulder girdle muscles. While the disease progresses, humeral, abdominal, pelvic girdle and foot dorsiflexor muscles often become involved as well (Figure 2) (8). Lower abdominal muscles are weaker than the upper abdominal muscles, causing a 'Beevor's sign', a physical finding specific for FSHD (Figure 3) (9).

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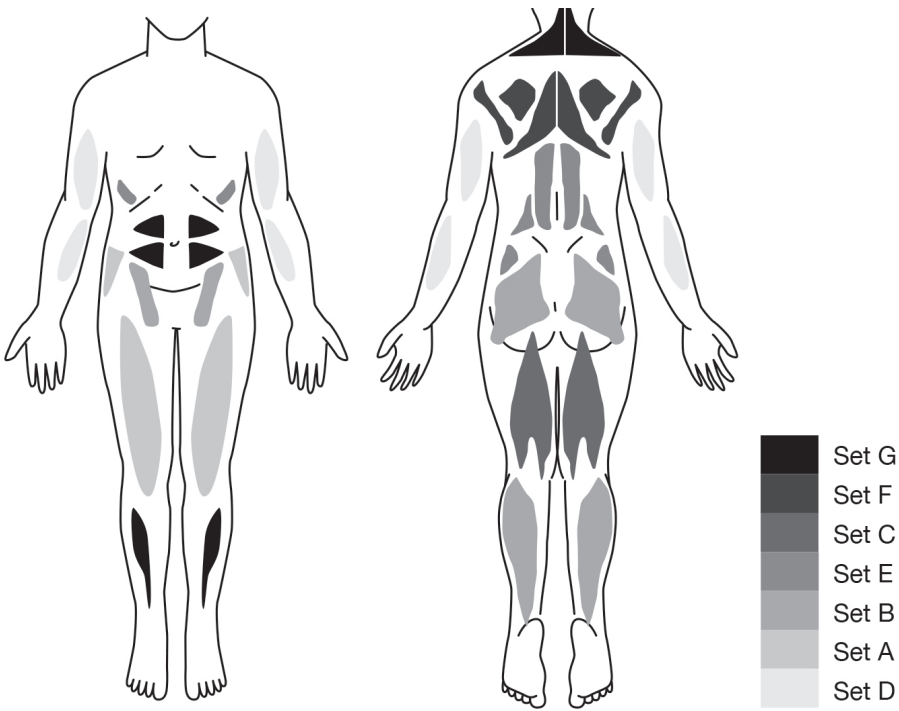
Figure 2 A visual representation of the muscle groups ordered by degree of fatty infiltration from red (most often affected) to yellow (least affected) (8)

The most commonly described extramuscular manifestations are hearing loss and retinal telangiectasias, occurring in 75% and 60% of the affected individuals, respectively (10).

The heart is not affected in most cases, although asymptomatic arrhythmias and conduction defects have been described (11). The median age of onset is around 17 years, but the onset of clinical symptoms varies from infancy to the seventh decade. The course of FSHD is usually slowly progressive, but the severity among patients is extremely variable, even within families, ranging from isolated facial weakness to severe generalized weakness, with approximately 20% of patients eventually becoming wheelchair-dependent. Many patients report a relapsing course, with long periods of quiescence interrupted by periods of rapid deterioration involving a particular muscle group, often heralded by pain in the affected limb. Most of the patients have a normal life expectancy (10).
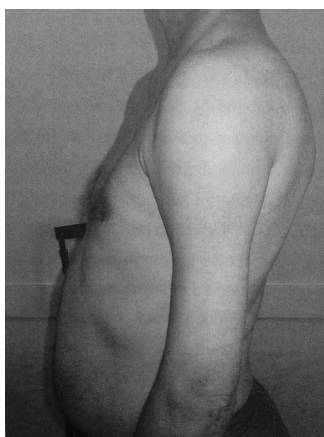
Figure 3 Beevor's sign

Many FSHD patients have a protruding abdomen because the lower abdominal muscles are more severely affected than the upper abdominal muscles. This asymmetrical weakness leads to Beevor's sign: upward displacement of the navel while flexing the neck. It is a typical finding for FSHD on clinical examination.

MUSCLE IMAGING IN FSHD

A typical characteristic of FSHD is the asymmetric and individual involvement of different skeletal muscles. In the last decade, substantial progress has been made in the understanding of the molecular genetics of FSHD (12). However, it is still unknown why the weakening of different muscles and muscle groups occurs at different rates and times. Moreover, there are no biomarkers for an objective assessment of the severity and progression of FSHD and to establish the effectiveness of treatments. Currently, muscle ultrasound is predominantly used as a screening tool for patients with suspected neuromuscular disorders, as it can

easily visualize intramuscular fibrosis and fatty infiltration. In the past, computer tomography (CT) has been used for unbiased and reliable assessments of skeletal muscle in FSHD patients (13). Nevertheless, magnetic resonance imaging (MRI) is nowadays preferred over CT as determination of therapy effectiveness in follow-up examinations would require multiple CT scans, with inherent radiation load. Furthermore, the sensitivity in the identification of fatty infiltration is higher for MRI compared to CT. With MRI a detailed picture of the anatomy of individual skeletal muscles or whole muscle groups can be obtained. In FSHD, MRI with T1 weighting shows fatty infiltration and changes in muscle volume of affected muscles. T2 weighted MRI can show inflammation and edema (14). Kan et al. developed a new MR method to quantitatively separate muscular and fat content in different muscles of the lower limb in patients with FSHD, using differences in T2 relaxation times of fat and muscle tissue, to provide an objective biomarker for individual muscle involvement (15). By using MRI, clinically useful biomarkers for disease progression and response to therapy could be established.

FATIGUE IN FSHD

Fatigue is one of the most commonly presented symptoms in primary care with a prevalence of 5-20% across different patient groups (16). Although chronic fatigue can lead to reduced psychosocial functioning, in the past fatigue was often neglected as a target for treatment, perhaps because it is difficult to assess and manage (17). In contrast to pain, fatigue can be experienced as positive, e.g. during and after sports. Such a sensation of fatigue is of short duration and will be resolved by rest. In contrast, chronic fatigue often accompanies medical illness, lasts longer than six months, is poorly relieved by rest, and is often not related to activity (18). Currently, fatigue is increasingly being recognized as a major clinical problem in many conditions and evidence-based treatment programs are now developed for e.g. patients with cancer, stroke and multiple sclerosis (19-21). Fatigue consists of several dimensions and, therefore, it is important to assess each dimension and to determine how the different dimensions are related. Experienced fatigue is assessed subjectively by means of questionnaires. In the absence of a universal definition of fatigue a large number of scales have been developed attempting to assess the nature, level and impact of fatigue in several populations, so no gold standard is to be expected. In the general literature more than 250 questionnaires to assess fatigue have been reported, of which 150 have been only used once (22).These scales differ from each other mainly in the construct that is assessed. For example, in the Fatigue Severity Scale (23) fatigue is regarded as a uniform construct as this scale focuses mainly on the experienced

impact of fatigue on daily life. However, unidimensional fatigue measures do not capture the full spectrum of fatigue as a multidimensional phenomenon. To assess fatigue more extensively, especially in research, multidimensional questionnaires are applied. An example of a multidimensional instrument is the Checklist Individual Strength (CIS), consisting of four subscales: subjective fatigue experience, concentration, motivation and subjective physical activity. The subscale experienced fatigue of the CIS (CIS-fatigue) assesses the level of experienced fatigue and has been frequently used in clinical studies. The CIS-fatigue consists of eight questions that have to be answered on a seven-point Likert scale (range 7-56). Severe fatigue is defined by a cut-off score of 35 or higher (24). The CIS-fatigue has been used to assess the level of fatigue in patients with FSHD in a cross-sectional study by Kalkman et al. It was found that more than 60% of the patients with FSHD experienced severe fatigue (1). In addition, being severely fatigued was associated with a lower level of social participation. Apparently, fatigue is a prevalent and a relevant problem in patients with FSHD.

REHABILITATION OF FATIGUE IN FSHD

Rehabilitation of people with neurological disabilities is a process aimed at enabling them to reach and maintain their optimal physical, sensory, intellectual, psychological and social activity level. Rehabilitation provides disabled people with the tools they need to attain and maintain independence and self-efficacy (25). In FSHD, muscle function is impaired and declines over time. A progressive loss of muscle strength and muscle endurance often leads to loss of functional abilities and mobility. Patients with FSHD identify poor mobility, fatigue and the emotional and social burden of the disease as the factors with the greatest impact on their lives (26). Fatigue may result in patients altering their lifestyles to avoid activities. Low physical activity levels may lead to even deconditioining, greater weakness and atrophy of skeletal muscles, which causes a vicious circle of disuse and increased fatigue (27).

In a longitudinal study Kalkman et al (28) built a model of perpetuating factors for fatigue in patients with FSHD using structural equation modelling. A total of 60 ambulatory patients were studied twice during an 18-months period. Experienced fatigue was assessed with the CIS-fatigue (24), while a multidimensional functional assessment was used to identify various dimensions relevant for fatigue: pain, muscle strength, physical activity, neuropsychological impairments, psychological distress, sleep disturbances, concentration problems, social functioning and social support, and quality of life. It appeared that lack of physical activity, sleep

disturbances and pain all contributed to experienced fatigue. Loss of muscle strength contributed to experienced fatigue through a lower level of physical activity. In addition, pain contributed to physical inactivity. Ultimately, experienced fatigue and physical inactivity both determined the level of social dependence and loss of participation. The model, presented in Figure 4, served as a basis for the treatment protocol used in this thesis.
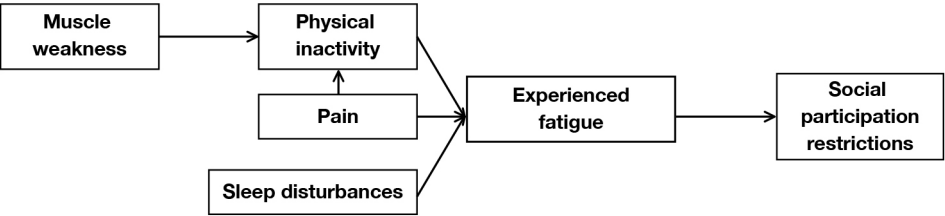
Figure 4 Model of perpetuating factors of fatigue for patients with FSHD

Source: Adapted from Kalkman et al. (28)

It was hypothesized that, in order to preserve functioning at the highest achievable level and to prevent the vicious circle of inactivity, two different therapeutic approaches can be followed: aerobic exercise therapy to promote physical activity and cognitive behavioral therapy to stimulate an active lifestyle yet avoiding excessive physical strain.

Aerobic exercise aims at maintaining muscle function and improving cardiorespiratory status to optimize physical capacity as a prerequisite for executing many activities in daily life. For a long time, individuals with muscle degeneration were discouraged to perform physical exercise based on fear for exacerbation of disease activity and damage to muscle fibers. However, recent studies have shown that exercise in patients with neuromuscular disorders is safe and, thus, applicable to patients with FSHD (29). Although the number of exercise studies in patients with neuromuscular disorders is increasing, the overall amount of studies is still scarce.

FSHD has a strong impact on psychosocial functioning as patients have to periodically re-adapt their daily life activities to living with a progressive illness. Illness cognitions and coping style influence the choice and level of activities and, hence, quality of life.

Because a cognitive-behavioral approach influencing illness cognitions and coping strategies has been proven successful for chronic fatigue syndrome (30) and post-cancer fatigue (19), it was expected to be efficacious for chronic fatigue in patients with FSHD as well. No previous studies used cognitive behavioral therapy to treat fatigue in FSHD.

THE FACTS-2-FSHD STUDY

Since there is still a long way to go before a treatment is expected that will decelerate or perhaps even cease disease progression in FSHD, interventions to treat the consequences of the disease are particularly important. This thesis reports the results of the FACTS-2-FSHD study (acronym for Fitness And Cognitive behavioral TherapieS for Fatigue and ACTivitieS in FSHD) which is the first model-based randomized clinical trial that evaluates the effects of aerobic exercise training (AET) and cognitive behavioral therapy (CBT) on chronic fatigue in patients with FSHD. These interventions are based on the above-mentioned model of chronic fatigue. The primary objective of this study was to evaluate the effect of both interventions on chronic fatigue in patients with FSHD as assessed with the subscale fatigue of the Checklist Individual Strength. The secondary objective was to evaluate the effects of each intervention on the known perpetuating factors of chronic fatigue in FSHD based on secondary outcome measures covering all domains of the International Classification of Functioning, Disability and Health (ICF). In addition, it was aimed to find clinically useful MRI biomarkers of disease progression and response to therapy in patients with FSHD.

The FACTS-2-FSHD study is one of the studies conducted within the FACTS-2-NMD consortium. FACTS-2-NMD stands for Fitness And Cognitive behavioral TherapieS for Fatigue and ACTivitieS in NeuroMuscular Diseases (www.facts2nmd.nl), a consortium funded by the Dutch Public Fund for Neuromuscular Disorders (Prinses Beatrix Spierfonds) and the Netherlands Organization for Health Research and Development (ZonMw) (grant nr 89000003).

AIMS AND OUTLINE OF THE THESIS

This thesis consists of two parts. The **first part** gives an overview of the prevalence, measurement and treatment of fatigue in neuromuscular disorders. The **second part** presents the results of the FACTS-2-FSHD study.

The following research questions will be addressed:

PART 1 FATIGUE IN NEUROMUSCULAR DISORDERS

1. What is the prevalence and relevance of fatigue in patients with muscular dystrophy?

    🚲 **Chapter 2** gives an overview of the prevalence of fatigue and consequences in muscular dystrophies.

2. How can we assess fatigue in patients with neuromuscular disorders?

    🚲 **Chapter 3** provides a core set of instruments for measuring fatigue in patients with neuromuscular disorders.

3. What is the evidence for exercise in muscle disease?

    🚲 A Cochrane review regarding the effects of strength training and aerobic exercise therapy in patients with muscle disease is reported in **chapter 4**.

PART 2 FACTS-2-FSHD STUDY

4. What are the effects of aerobic exercise therapy and cognitive behavioral therapy on chronic fatigue in patients with FSHD?

    🚲 The protocol of the FACTS-2-FSHD trial, which aims to decrease experienced fatigue by AET and CBT, is described in **Chapter 5**. The main results of the trial are presented in **Chapter 6**.

5. Can we discover structural abnormalities in skeletal muscle of FSHD patients that may serve as biomarkers for disease progression and response to therapy?

In **chapter 7**, MRI measurements are used to provide more information about the underlying pathobiology of FSHD. **Chapter 8** describes the effects of AET and CBT on the progression of fatty infiltration in the thigh muscles of patients with FSHD.

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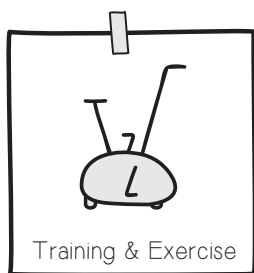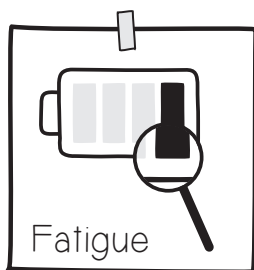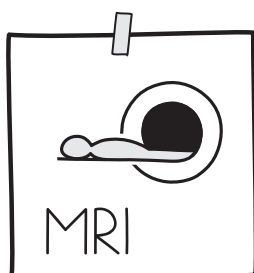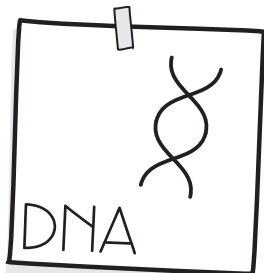
PART 1

FATIGUE IN NEUROMUSCULAR DISORDERS
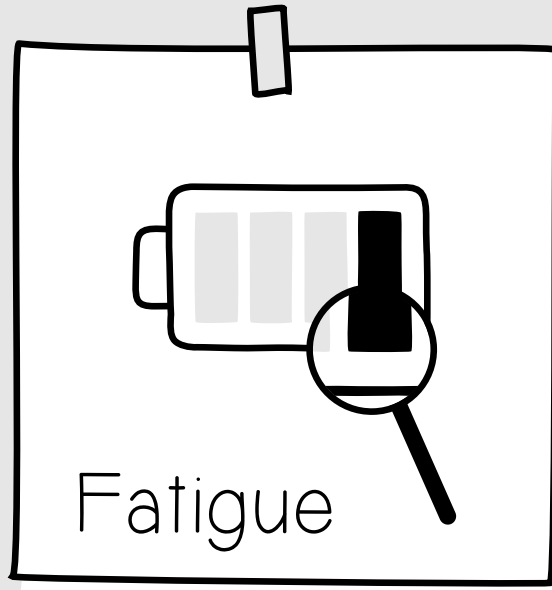
Fatigue

CHAPTER 2

MUSCLE FATIGUE IN MUSCULAR DYSTROPHIES

Nicoline B.M. Voet
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George W. Padberg
Baziel G.M. van Engelen

OBJECTIVES

The aim of this chapter is to provide an overview on:

- the prevalence and assessment of fatigue in muscular dystrophies
- the pathophysiological determinants of fatigue in muscular dystrophies
- the possible treatment options of fatigue in muscular dystrophies

INTRODUCTION

The aim of this chapter is to provide an update on the prevalence, relevance, causes and treatment of fatigue in muscular dystrophies. In a study by McDonald et al., the three problems most frequently cited as "very significant" by patients with slowly progressive neuromuscular disease (n = 811) were muscle weakness (57%), difficulty exercising (43%), and fatigue (40%) (1). In a study by Kalkman et al., 61% of patients with facioscapulohumeral dystrophy (n = 139) and 74% of patients with myotonic dystrophy (n = 322) were "severely fatigued" (2). The muscular dystrophies are an inherited group of more than 30 distinct progressive disorders resulting from defects in a number of genes required for normal muscle structure and function. They are characterized by progressive loss of muscle strength and integrity and they have a variable distribution and severity (3). We will, however, limit our review to those main types of diseases which are most frequent: Duchenne and Becker muscular dystrophy, myotonic dystrophy type 1, facioscapulohumeral muscular dystrophy and the limb girdle muscular dystrophies. A more extensive overview of muscular dystrophies can be found in Engel and Franzini-Armstrong (4).

In this chapter, we will distinguish two main types of fatigue (Table 1):

Table 1 Dimensions and definitions of fatigue as used in this chapter

Muscle fatigue, or physiological fatigue, can objectively be assessed in a laboratory setting and is defined as the total amount of voluntary loss of force during a sustained maximal voluntary muscle force (MVC). It contains both peripheral and central components, a distinction that is based on whether the loss of capacity to generate force originates from the muscle system or the central nervous system.

Peripheral fatigue can be determined as the loss of force during constant electrical stimulation, applied to the motor nerve or motor endplate during a sustained MVC.

Central fatigue can be determined as an increase in central activation failure during exercise. Central activation failure (CAF) is defined as submaximal central activation. CAF can be measured by the "twitch interpolation technique". If the central activation is submaximal, the electrical stimulation, applied to the motor nerve or motor endplate during a sustained MVC, will result in an increased exertion of force compared to exertion of force without electrical stimulation, demonstrating CAF. CAF can be present already at the start of a sustained MVC (Schillings et al. 2007).

Experienced fatigue is by definition a subjective entity and can be assessed only by self report, for example with the subscale fatigue of the Checklist Individual Strength, and does not necessarily correlate with physiological fatigue. Experienced fatigue has many dimensions: for example activity limitations in daily life, physical inactivity, sleep disturbances, concentration problems, loss of social participation, psychological distress, sense of control over fatigue, cognitions about the possible cause of fatigue, and pain.

Physiological fatigue, or muscle fatigue, which has been defined as a reduction in MVC during exercise. Experienced fatigue, on the other hand, is the subjective feeling of fatigue. Muscle fatigue is not necessarily accompanied by experienced fatigue, or vice versa.

High-quality studies about fatigue in muscular dystrophy are scarce. Nevertheless, after a general introduction on muscular dystrophies, addressing both clinical and pathophysiological aspects, the prevalence of experienced fatigue in muscular dystrophies in the literature will be critically reviewed and the putative underlying pathophysiological mechanisms of muscle fatigue and experienced fatigue will be outlined. Finally, literature about treatment of muscle fatigue and experienced fatigue in muscular dystrophies will be reviewed and recommendations for future

research will be made. Throughout the chapter, the scientific knowledge will be illustrated by a clinical case report that describes the experienced fatigue of a 59 year old man with facioscapulohumeral dystrophy, Mr. A.

DYSTROPHINOPATHIES

Duchenne muscular dystrophy (DMD) is the most common form of the human muscular dystrophies. Becker muscular dystrophy (BMD) is a less frequent and more benign form of the disease. The incidence of DMD is approximately 1 in 3.500 live male births. By comparison, BMD is found in 1 in 30,000 male births (5). Both are X-linked recessive disorders and are caused by a mutation in the DMD gene which is located on chromosome Xp21 and encodes for the production of dystrophin. One third of the cases are due to spontaneous mutations (6). The primary abnormality in DMD is the lack of dystrophin. In BMD, the protein is reduced in amount or abnormal in size. Dystrophin is a 427 kiloDalton protein normally found at the cytoplasmic face of the muscle cell surface membrane, functioning as a component of a large, tightly associated glycoprotein complex (7). In its absence, the glycoprotein complex is digested by proteases. This may initiate the degeneration of muscle fibers, resulting in muscle weakness and potential mechanical injury from tissue stress in rest and during exercise (8-10).

Diagnosis is suspected by characteristic clinical findings among which progressive symmetrical muscle weakness is the most important, affecting proximal limb muscles more than the distal muscles. Initially, only lower limb muscles are affected accompanied by pseudohypertrophy of the calf muscles. Common musculoskeletal complications are kyphoscoliosis and muscle contractures. Because dystrophin is also found in the heart, brain, and the smooth muscles, frequent concomitant manifestations are cardiomyopathy and mental retardation (11).

In DMD, the clinical symptoms first present between 3 and 5 years of age, and patients generally lose ambulation between 7 and 12 years. In the past, death usually occurred from cardiac or respiratory causes in the late teens or early twenties. But recently, respiratory support can prolong survival into the fourth decade (12). The diagnosis is supported by a family history suggestive of X-linked recessive inheritance (4) or by dystrophin immunostaining of muscle tissue (6, 13, 14) Serum creatine phosphokinase (CK) level is generally increased to levels that are 50-100 times the reference range (i.e. as high as 20,000 mU•mL-1). The diagnosis is confirmed by identifying abnormalities in the dystrophin gene by mutation analysis of DNA from peripheral blood leukocytes (6).

In BMD, the distribution of muscle wasting and weakness is closely similar to that in DMD, but the course of the disease is more benign and far less predictable, with first clinical symptoms presenting around 12 years. Many patients remain ambulatory into adult life (3, 6).

No curative treatment is available for both diseases, although first attempts are made: the gene transfer technique by intramuscular injection of an antisense oligonucleotide is under development (15), but several hurdles still need to be taken (16). Therefore, emphasis currently is on respiratory care, treatment of cardiological complications and optimizing the quality of life by symptomatic physiotherapeutic and medical treatments (17). There is evidence that corticosteroid therapy in DMD can reduce speed of decline of muscle strength and function (18, 19).

MYOTONIC DYSTROPHY

Myotonic dystrophy (DM) is the second most common muscular dystrophy. There are two major forms: DM1, also known as Steinert's disease, and DM2, a multisystem disease, also known as Proximal Myotonic Myopathy (PROMM). In this chapter, we will limit the discussion to DM1, which is more frequent.

DM1 is divided into congenital, classical, and minimal phenotypes according to the age of the symptom onset and disease severity. The congenital form of DM1 will not be further considered in this chapter, see Engel and Franzini-Armstrong (4). The prevalence of DM1 is approximately 1 in 8,000 in the general population (20). DM1 is an autosomal-dominant disorder, of which the molecular basis is expansion of an unstable repeat sequence in a non-coding part of the dystrophia myotonica protein kinase gene (DMPK gene) on chromosome 19. The repeat expansion enlarges with each generation, which leads to earlier onset and increased severity of symptoms with each affected generation, a phenomenon which is known as "anticipation" (21). There is increasing support for the theory that disruption of RNA metabolism, which has effects on many other genes, explains the multisystemic nature of the disease (22).

DM1 is clinically characterized by muscle weakness of the distal limbs, progressing to the proximal limbs with gradual occurrence of myotonia (delayed relaxation after muscle contraction). Weakness occurs most frequently in facial muscles, the distal muscles of the forearm, and the ankle dorsiflexors with onset of symptoms in the second, third or fourth decade (23). Associated findings include muscle pain, cognitive and psychological changes, cataract, cardiac conduction defects and endocrine disorders (20, 24, 25). Excessive daytime sleepiness is found in about one-third of patients (26, 27).

The diagnosis can be suspected clinically by a positive family history and by identifying the symptoms mentioned above. Specific genetic testing to demonstrate the presence of an expanded CTG repeat in the DMPK gene is the gold standard for the diagnosis of DM1 (20). Life expectancy is reduced for patients with DM1. Respiratory insufficiency and cardiac diseases are the most common causes of death (28-30). There is no disease-modifying therapy available for the treatment of DM1. Therefore, treatment is symptomatic (31).

FACIOSCAPULOHUMERAL DYSTROPHY

Facioscapulohumeral dystrophy (FSHD) is the third most common muscular dystrophy. The estimated prevalence is 1 in 20,000 persons (32). FSHD is an autosomal dominant disease. It is associated with subtelomeric contraction of chromosome 4q, with loss of tandem repeat-units. In general, the disorder is more severe in a patient with a lower number of repeats. The pathogenetic mechanisms in FSHD are unknown. The presence of some extramuscular manifestations in FSHD suggests the involvement of a gene with pleiotropic effects or, alternatively, the involvement of multiple genes (33). FSHD derives its name from the muscle groups that are mainly affected first: facial and shoulder girdle muscles. During disease progression humeral, abdominal, pelvic girdle and foot-extensor muscles can become involved as well (32). Lower abdominal muscles are weaker than the upper abdominal muscles, causing a "Beevor's sign", a physical finding specific for FSHD (34). Most commonly described extramuscular manifestations are the high-frequency hearing loss and retinal telangiectasias, occurring in 75% and 60% of affected individuals, respectively (33). The heart is not affected in most cases, though arrhythmias and conduction defects have been described (3).
The median age of onset is around 17 years, but the onset of clinical symptoms varies from infancy to the seventh decade (32).

Although the exact gene defect or genetic mechanism is not yet known, a DNA test is available for FSHD which detects a specific deletion in chromosome 4q35. This diagnostic test is abnormal in 95 to 98 percent of typical FSHD cases (35-37).

The course of FSHD is usually slowly progressive but the severity among patients is extremely variable, ranging from isolated facial weakness to severe generalized weakness, with approximately 20 % of patients eventually becoming wheelchair-dependent (32). Many patients report a relapsing course with long periods of quiescence interrupted by periods of rapid deterioration involving a particular muscle group, often heralded by pain in the affected limb. Most of the patients have a normal life expectancy (33).

Currently, there is no genetic or pharmaceutical curative treatment available for FSHD. Only two randomized controlled trials have been published. Recent trials of albuterol, also known as salbutamol (38, 39), folic acid and methionine (40), and creatine, a dietary supplement for building muscle (41), did not confirm or refute a significant effect of either of these treatments (42). The mainstay of management is, therefore, treatment of symptoms, prevention of secondary problems, and improvement of functional abilities and quality of life (33).

LIMB GIRDLE MUSCULAR DYSTROPHIES

The limb girdle muscular dystrophies (LGMD) are a group of disorders which are historically grouped together because of the shared clinical feature of predominant involvement of the "limb-girdle" (pelvic and shoulder) musculature. However, it is recognized that there is a broad heterogeneity of presentation and muscle involvement in the LGMD group (43). The overall frequency has been estimated to be 1: 14,000 – 1: 200,000 (5). Most cases of LGMD are inherited in an autosomal recessive fashion (44). However, families with an autosomal dominant pattern of inheritance have also been described, which probably account for about 10% of all LGMDs (45). The emergence of a LGMD phenotype can result from mutations in any of, at least, 19 different genes (46). The discovery of genetically distinct subtypes has redefined the classification of LGMD and has led to a nomenclature designating the autosomal dominant form as LGMD1A, 1B, 1C, etc, and the autosomal recessive form as LGMD2A, 2B, 2C, etc (45). The proteins causing LGMD have a wide range of localization across the muscle fiber, from sarcolemma to nuclear envelope, with various functions (43, 46).

Weakness may affect proximal muscles of the shoulder girdle (scapulohumeral type), the pelvic girdle (pelvifemoral type), or both. Neck flexor and extensor muscles may be concurrently involved. Facial weakness, when present, is usually mild and, in most cases, totally absent. Even in mild cases, there is preferential weakness and atrophy of the biceps muscle.
Distal muscle strength is usually preserved, even at the late stage of the disease. Selectivity of muscle involvement and clinical characteristics such as hypertrophy of the calves or tongue, and late stage cardiac complications are associated more or less specifically with each of the different forms (4).

The single constant biochemical abnormality in LGMD is the elevation of the CK level. In autosomal recessive types of LGMD, serum CK is always increased, up to 200 times the normal range. DNA analysis to detect a mutation in the affected gene(s) is the gold standard of diagnosis (47). Reported age of onset of LGMDs

varies among the different mutations and is between 1 and 50 years, although some patients may be asymptomatic. Compared with the autosomal dominant type, autosomal recessive LGMD is usually associated with earlier age of onset, more rapid progression, and relatively high CK values. Morbidity and mortality rates vary, but with early onset the course is generally rapid (4). Treatment is supportive and consists of physical therapy, assistive devices and monitoring of respiratory function and cardial complications. Treatment is generally aimed at prolonging survival and improving quality of life (46).

Clinical case: disease description

Mr. A is a 59 year old man who broke his clavicle in a football game when he was 18 years old. A year after the accident he went back to his general practitioner, because symptoms of pain and decreased functioning of his shoulder did not disappear. He was referred to a neurologist, who clinically diagnosed a "muscle disease" when he was 19 years old. At that time, he knew that his mother, who was wheelchair-dependent, had a "muscle disease", but neither the diagnosis, nor the prognosis of her condition was known. Decades later, his neurologist told him he had a muscle disease which was known as "Landouzy–Dejerine", the former name of FSHD. The diagnosis FSHD was genetically confirmed 30 years later. At that time, an autosomal dominant inheritance pattern could be recognized in his family. Many persons in every generation appeared to be affected by the disease.

Mr. A experiences a relapsing course of FSHD with long stable periods followed by periods of clear deterioration. Currently, facial, shoulder girdle, humeral, abdominal, pelvic girdle and foot-dorsiflexor muscles are involved. He is still ambulant but his unaided walking distance is restricted to approximately 100 meters. Outdoor he uses a rollator, which increases his walking distance to 250 meters. He is very afraid of becoming wheelchair-dependent, just like his mother. Mr. A lives together with his wife in an apartment at ground level. He works four days a week as an IT specialist and spends a lot of time in volunteer activities. He plays the saxophone in a band.

EXPERIENCED FATIGUE

ASSESSMENT OF EXPERIENCED FATIGUE

Distinguishing experienced fatigue from muscle weakness, the key feature in muscular dystrophy, may be difficult. Asking patients to describe their

fatigue will lead to several descriptions, varying from sleepiness, weakness, exercise intolerance to exhaustion. Hence, experienced fatigue is, therefore, a multidimensional concept with possible contributions of, for example physical, cognitive and motivational factors (Table 1). Although experienced fatigue is difficult to define, it still is a valuable concept which can be reliably measured by using questionnaires. An often used questionnaire for the experience of fatigue and its behavioral consequences is the Checklist Individual Strength (CIS). The CIS is consists of four subscales: one scale for experienced fatigue, so called "CIS-fatigue", and three scales for reduction in motivation, physical activity and concentration, respectively. Higher scores indicate higher levels of fatigue, more concentration problems, a greater decrease in motivation and lower levels of activities (48). The Abbreviated Fatigue Questionnaire (AFQ) is another short, reliable, and easy-to-use instrument to determine the intensity of a patient's experienced fatigue. It consists of four questions that have to be answered on a 7-point Likert scale. A lower total score indicates a higher degree of fatigue (49).

PREVALENCE AND IMPACT OF EXPERIENCED FATIGUE

Kalkman et al. measured the prevalence of "severe experienced fatigue" in of 598 neuromuscular patients, among which 139 patients with FSHD and 322 patients with DM. Both patient groups experienced high levels of fatigue (2). The mean CIS-fatigue score in the FSHD group was 36.5 (SD 12.5) and in the DM group 40.4 (SD 11.8). In the FSHD group 61% of patients were "severely fatigued" (determined by a CIS-fatigue score equal or above 35). In the DM group, this percentage was 74. In both groups, age showed low but significant correlations with fatigue severity, indicating that, in general, older patients experienced somewhat greater fatigue. Severely fatigued patients scored lower on all Short Form-36 (SF-36) scales than the non-severely fatigued patients, suggesting a relation between experienced fatigue and activity limitations. There appeared to be several differences between DM and FSHD patients. Patients with DM had higher scores for experienced fatigue, reported greater problems with concentration, and had more difficulties with initiative and planning than patients with FSHD. In FSHD patients and DM patients, social functioning was related to fatigue severity.
Irrespective of its cause, fatigue has a major impact on daily functioning and quality of life (50, 51). For example, in a study by van der Werf in patients with DM (n = 32) and FSHD or LGMD (n = 20), severe fatigue was associated with greater levels of psychological distress and more physical and psychosocial limitations, as measured with the Sickness Impact Profile (SIP), the Symptom Checklist-90 (SCL-90) and the Beck Depression Inventory Primary Care (BDI-PC) (52). In the study by Kalkman et al. severely fatigued patients with FSHD or DM also had lower scores

on all subscales of the SF-36, which monitors disease burden.

This suggests a relation between experienced fatigue and the level of activity and social participation (4). Apparently, fatigue is not only a frequent, but also a relevant problem in muscular dystrophy.

> **Clinical case: experienced fatigue**
>
> *Mr A has suffered from fatigue since the age of 40. He considers his fatigue and muscle pain to be the most relevant and disabling consequences of his disease. He defines his fatigue as a lack of energy which restrains him from activities. After walking approximately 100 m, he has to stop because of severe fatigue and muscle pain. These symptoms are comparable with the exhaustion he felt after playing football in his younger years. That type of exhaustion, however, felt positive, in contrast to the negative feeling associated with the present fatigue. Fatigue has a significant and deleterious impact on his life that goes beyond the other symptoms of FSHD. It takes almost two hours to prepare himself for work every morning. After he has dressed, he often falls asleep due to exhaustion. He can only travel by car because other forms of transport are too strenuous. He describes himself as a "healthy mind in an aged body".*

DETERMINANTS OF FATIGUE

As fatigue in muscular dystrophy is a multidimensional concept, (see assessment of experienced fatigue and Table 1), it is important to understand factors that contribute to fatigue. Based on such an analysis, preventive and therapeutic interventions can be developed. The critical pathophysiological determinants of muscle fatigue and experienced fatigue will, therefore, be described in the next section.

PATHOPHYSIOLOGICAL STUDIES OF MUSCLE FATIGUE

Because of practical reasons, pathophysiological studies depend to a large extent on animal models. A review of Wineinger et al. summarizes the literature regarding the physiological fatigue characteristics of skeletal muscles in animal models of muscular dystrophy (53). Muscle fatigue in animal studies was expressed as a percentage of initial force, i.e. physiological fatigue. Force was measured by recording the action potential (AP) of muscles and muscle-evoked tension. Two rodent models (mdx mouse and dystrophic hamster) have been studied most extensively. The dystrophic hamster, lacking normal sarcoglycan, was used as a

model for LGMD. The mdx mouse lacks dystrophin, and was therefore considered a model for DMD.

Significant variability has been observed before in studies of muscle fatigue in dystrophic animals, which may be due to different experimental conditions. Because of this variability, it is difficult to evaluate muscle fatigue in animal models of muscular dystrophy. Still, some trends can be recognized (Table 2).

Table 2 The difference in fatigability of dystrophic animal muscles compared to healthy animal muscles can be explained by differences in muscle fiber types

Muscle fiber type	Fatigability dystrophic animal muscles compared to healthy animal muscles.
Type I (slow-twitch, oxidative)	↓/ =
Type IIA (fast-twitch, oxidative)	=
Type IIB (fast-twitch, glycolytic)	↑

The dystrophic soleus muscle fatigued more slowly or at the same rate as that of healthy animals. The soleus is largely composed of slow-twitch type I oxidative muscle fibers and is considered to be fatigue resistant. Histological studies showed an increase in the proportion of type I muscle fibers in the dystrophic soleus muscle, which could explain the increased resistance to fatigue. The dystrophic extensor digitorum longus (EDL) was weaker than in healthy animals and generally more fatigable. The EDL muscle has a majority of type IIB fibers which are easily fatigable. Pagala et al. described that type IIB dystrophic muscle fibers are more susceptible to degeneration, in contrast to type I muscle fibers (54). No difference was found in fatigability between healthy and dystrophic diaphragm muscles. The diaphragm is composed of fast oxidative IIA muscle fibers, which are relatively fatigue resistant. It appears that difference in fatigability of dystrophic animal muscles compared to muscles of healthy animals can largely be explained by differences in muscle fiber types (Table 2).

Apparently, type I, in contrast to type II muscle fibers of dystrophic animal muscles have the potential to regenerate. Because aerobic training increases the proportion of type I muscle fibers and, with that, fatigue resistance of healthy muscles, aerobic training could be effective in decreasing fatigability of dystrophic muscles, as well through the same mechanism (55).

Increased muscle fatigue has often been attributed to a decrease in the metabolic potential of the individual muscle fibers. It is known that the levels of some energy metabolites like creatine are decreased in muscular dystrophies such as DMD (56, 57) which may aggravate muscle weakness and muscle fatigue. Interestingly, in some types of LGMD, in which muscles are less severely affected, creatine does not seem to be decreased, indicating that the level of creatine may serve as a biomarker for the severity of muscle weakness and muscle fatigue (58). Furthermore, the decrease in concentrations of other metabolites such as choline and lactate was less severe in LGMD compared to DMD suggesting that these metabolites could also be potential biomarkers (57).

In summary, these reports indicate that abnormal metabolite profiles could serve as specific biomarkers to characterize the severity of muscular dystrophies.

PERIPHERAL VERSUS CENTRAL FATIGUE

Until recently, the emphasis in clinical research in muscular dystrophies was on peripheral fatigue (Table 1). However, not only peripheral impairments, but also changes within the central nervous system could be responsible for increased fatigue. Schillings et al. first investigated central aspects of physiological fatigue in patients with muscular dystrophy (59). Both peripheral and central aspects of fatigue were determined during a sustained maximum voluntary contraction (MVC) of elbow flexion in patients with FSHD (n=65) and DM (n=79) (Figure 1).

Unexpectedly, overall physiological fatigue and peripheral fatigue were smaller in neuromuscular patients compared with healthy controls. Moreover, in patients with FSHD and DM, physiological fatigue did not correlate with the level of experienced fatigue. In contrast, Schulte-Mattler et al. described excessive peripheral fatigue in a mixed group of neuromuscular disorders, among which FSHD and DM (60). This discrepancy may be explained by a difference in the exercises. The type of exercise in the study by Schillings et al., i.e. isometric contraction at maximal force level, is hardly ever required in daily life and may also decrease blood supply. Schulte-Mattler et al. elicited fatigue by intermittent and non-tetanic contractions to avoid blood vessel occlusion. This type of exercise may be clinically more relevant and valid for measuring physiological fatigue. CAF and central fatigue in the study by Schillings et al. were measured by the twitch interpolation technique (See chapter 2) (61). Central fatigue was minimal in all groups and did not differ between groups nor did it have any relation with experienced fatigue. Remarkably, CAF at the start of sustained MVC was enlarged in patients compared to controls. CAF in patients was related to the level of experienced fatigue. An increased

CAF further decreases the maximal voluntary force in patients with muscular dystrophy. The cause of this decreased central activation cannot be determined by currently available techniques. It could be that the activation pattern of the central nervous system is not able to compensate for the peripheral problems in muscular dystrophies. The increased CAF could also be considered a beneficial adaptation, which prevents the affected muscles from excessive fatigue.
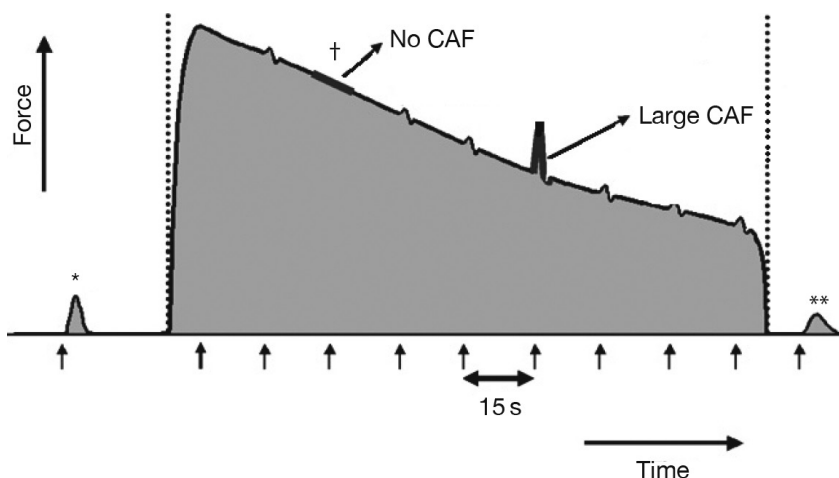
Figure 1 Schematic representation of peripheral and central fatigue

The figure shows the decline over time (within 2 min) of the maximum voluntary force (on the Y-axis), which is peripheral fatigue. The arrows indicate the moments of superimposed electrical endplate stimulation. The twitch interpolation may induce increments in muscle force with examples of a negligible (†) and a large CAF (#). A (near) absent response indicates a full voluntary activation of the muscle. The "at-rest twitches" are visible before (*) and following (**) the contraction, with the post-experimental twitch being clearly lower, indicative of peripheral fatigue. Source: Adapted from Zwarts et al., 2008. This figure is not the registration of an individual patient.

VICIOUS CIRCLE OF PHYSICAL INACTIVITY

Fatigue may result in patients altering their life-styles to avoid activities. Low physical activity levels may lead to even greater weakness and atrophy of skeletal muscles, which causes a vicious circle of disuse and weakness. Physical inactivity in turn can lead to chronic cardiovascular and muscle deconditioning and increased cardiovascular health risks (1). For example, the maximal oxygen uptake (VO2max) is abnormally low in patients with muscular dystrophy (62).

Body-composition measurements in muscular dystrophy patients by various methods indicate reduced fat-free mass (FFM) and increased adiposity in these patients relative to able-bodied control subjects of comparable ages and body weights (63, 64). The excess body fat of muscular dystrophy patients additionally impairs mobility and further increases the risk of cardiovascular disease.

In a study by McCrory et al., resting energy expenditure (REE) and total daily energy expenditure (TEE) were measured by indirect calorimetry and heart rate monitoring, respectively (65). Relatively active muscular dystrophy patients (FSHD, LGMD, DM and BMD) did not differ in REE, but had a lower estimated TEE. They also had a higher energy cost of physical activity than able-bodied subjects of the same gender who were similar in age and weight, even after adjustment for FFM differences. It is possible that the lower amount of time spent in physical activity by muscular dystrophy patients can be attributed to the higher energy cost. An alternative explanation is that persons with muscular dystrophy avoid physical activity, because of the widespread belief that too much strain on the muscles will accelerate the disease process (overwork weakness). Fear of physical activity, or fear to damage the muscle, may also contribute to the reduced central activation in patients with muscular dystrophy as described in the section peripheral versus central fatigue. Irrespective of its cause, physical inactivity should be discouraged in muscular dystrophy patients, because of an increasing risk of cardiovascular disease and muscle deconditioning.

PERPETUATING FACTORS OF EXPERIENCED FATIGUE

Experienced fatigue can be regarded as a multimodal concept, with a wide variety of contributing factors in patients with muscular dystrophy. These factors can be categorized into predisposing, precipitating and perpetuating factors. Predisposing factors include the presence of muscular dystrophy, whereas precipitating factors include acute physical stresses such as a concomitant disease or a period of relatively deterioration of muscle function. These factors cannot be treated, in contrast to perpetuating factors, which contribute to the continuation of experienced fatigue. Kalkman et al. used a longitudinal design to investigate the perpetuating factors of experienced fatigue in patients with FSHD (n = 60) and DM (n = 70) (66). Structural equation techniques, also referred to as "causal modeling" were used. Based on longitudinal data, separate models for FSHD and DM were developed. The model of perpetuating factors of experienced fatigue in FSHD differed from the model for DM, the main difference being physical (in)activity and pain. The model fit was best for FSHD (Figure 2).

Muscle weakness → Physical inactivity

Pain

Sleep disturbances

Experienced fatigue

Social participation restrictions
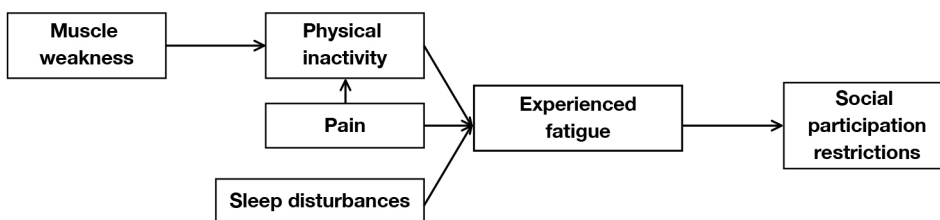
Figure 2 Adjusted model of perpetuating factors of experienced fatigue in patients with FSHD (n = 60)

Severe muscle strength, (self-reported) physical inactivity, pain and sleep disturbances were significantly associated with the level of experienced fatigue.

In FSHD, the level of physical (in)activity has a central place in the model. Lower levels of physical activity contribute to higher levels of experienced fatigue and, through that, to restrictions in social participation. The level of physical activity is directly and negatively influenced by loss of muscle strength. In addition, pain complaints influence levels of experienced fatigue both directly and indirectly by decreasing physical activity. In contrast, in DM, physical activity and pain did not differ between patients with and without severe experienced fatigue and, therefore, did not significantly contribute to experienced fatigue.

Yet, sleep disturbances lead to higher levels of experienced fatigue in both FSHD and DM patients. The observed patterns of perpetuating factors are unique for FSHD and DM, and are different from the model of experienced fatigue in chronic fatigue syndrome (48). They can be used as a basis to develop evidence-based interventions to reduce fatigue. Specific attention should be paid to sleep disturbances in both patient groups. Specifically in FSHD, treatment of fatigue should also be directed at increasing physical activity and reducing pain complaints.

EXPERIENCED FATIGUE AND PSYCHIATRIC DISORDERS

Fatigue is a characteristic of a number of affective disorders, and an association between experienced fatigue and psychiatric symptoms has been reported in a number of central nervous system disorders, including Parkinson's disease and multiple sclerosis (67, 68). In this perspective, it is relevant to know whether psychiatric comorbidity is associated with fatigue severity in muscular dystrophies. Although in the study by Kalkman et al. (see section on prevalence and impact of experienced fatigue) severe experienced fatigue was related to higher levels of psychological distress in both patients with FSHD and DM, most of the severely fatigued patients did not fulfill the operational criteria of depression (4). The authors

argued that severe experienced fatigue can, therefore, not be seen as merely a sign of depression. In a later study by Kalkman et al. using the Structured Clinical Interview for DSM-IV axis 1 disorders, and Beck Depression Inventory (BDI) lifetime and current psychiatric disorders (mood disorders, anxiety disorders and substance-related disorders) were equally prevalent in a large cohort of DM and FSHD patients, and were equally or even less present than these disorders in the general (Dutch) population (69, 70). The most common psychiatric disorders were depression and phobias. Psychiatric comorbidity was not associated with fatigue severity or muscle strength in the various neuromuscular disorders. In conclusion, psychiatric comorbidity is not an explanation for experienced fatigue in FSHD and DM.

Clinical case: perpetuating factors of fatigue

Mr A experiences fatigue during activities of daily life, work and leisure, but also when reading a book due to concentration problems. He easily falls asleep by day. At night, his sleep is often disturbed by muscle pain. In the past, when he was less physically disabled, he exercised at a low intensity. In his youth, he played football. In adult life, he practised swimming once a week and, later on, physical fitness, but avoided excessive training because of fear of overuse. Nevertheless, many years ago he altered his lifestyle. He stopped swimming and playing football. Currently, he is physically inactive and in a vicious circle of disuse and weakness. His physical inactivity results in muscle and cardiovascular deconditioning and obesity. Altogether, he is at risk for cardiovascular disease. Seven years ago, he experienced an ischemic cerebrovascular incident, which further increased his experienced fatigue.

TREATMENT OF FATIGUE

Most treatment studies in patients with muscular dystrophy do not describe the efficacy of the intervention in terms of decreasing muscle fatigue or experienced fatigue. Nevertheless, we will provide a critical overview of the possible treatment options with respect to fatigue in these patients. Treatment strategies that will be reviewed include physical exercise training, drug treatment and cognitive behavioral therapy.

TRAINING STUDIES IN ANIMALS

Extrapolating data from animal studies to humans must be done with caution, because there are large differences in biomechanical properties and phenotypic expression of the dystrophic disorder between humans and, for example, the mdx mouse. Nevertheless, it may still be valuable to consider animal studies first, since unique information can be obtained (53, 71). Exercise training in animals mainly consisted of high-repetition aerobic-type activities like swimming, treadmill running or voluntary-wheel running. Two reviews described that dystrophic animals had a normal (and beneficial) adaptation to mild, voluntary submaximal aerobic exercise, which generally included an increase in muscle strength per cross-sectional area of muscle tissue and a reduction in muscle degeneration. The oxidative capacity and the proportion of oxidative fibers were increased, especially in slow-twitch muscles and in the muscles that were not severely affected by the dystrophy (53, 72). Aerobic training apparently increases the amount of type I muscle fibers, as hypothesized earlier in this chapter (see section on pathophysiological studies of muscle fatigue). Younger animals tend to benefit more from exercise studies than older animals. The muscles of young dystrophic mdx mice have a greater rate of recovery of force production than those of older mdx mice. Histological and contractile studies suggest that this difference is due to an increased regenerative capacity in young dystrophin-deficient mdx mice, which is lost in older mdx mice (71, 73).

Carter et al. reviewed studies of exercise training and contraction-induced muscle-injury in animal models of muscular dystrophy (72). A majority of the studies in both normal and dystrophic animals showed that untrained eccentric exercise (lengthening of the muscle during contraction) may injure the contractile and cytoskeletal components of the muscle fibers. During eccentric exercise, sarcomeres are stretched and the actin and myosin filaments are pulled apart, leading to disruption of the thick and thin filament array and subsequent damage to cytoskeletal proteins. The inability to quickly repair a disruption of the membrane causes an elevation in intracellular calcium concentration, which triggers calcium-activated degradation pathways and further structural damage. This damage results in fiber degeneration followed by inflammation and, eventually, fiber regeneration. Probably because of their increased regenerative capacity, muscles of younger mdx mice recovered more rapidly than those of older mdx mice (74-77). Based on these animal studies, one can conclude that submaximal aerobic exercise training can be beneficial. However, eccentric exercise training should be avoided.

TRAINING STUDIES IN MUSCULAR DYSTROPHY PATIENTS

In the past, many patients with muscular dystrophy were advised not to exercise because of the belief that too much exercise might lead to "overuse weakness" (78-80). Yet, in their Cochrane review on muscle strength training and aerobic exercise training for patients with muscle diseases, van der Kooi et al. concluded that moderate intensity strength training in DM and FSHD appeared not to be harmful, although there was insufficient evidence to establish its benefit (81). This conclusion was based on merely two randomized clinical trials (RCTs) (38, 82). When RCTs are scarce, evidence from nonrandomized studies and other designs, such as pre-post studies or case-control studies, may be particularly relevant (83). For this reason, Cup et al. reviewed not only RCTs, but also controlled clinical trials and other designs of sufficient quality, using the list by van Tulder et al. (84, 85). All types of exercise therapy and other physical therapy modalities were included for patients with muscular dystrophy, among which patients with FSHD, LGMD, DM and DMD. Cup et al. also concluded that exercise training is not harmful in muscular dystrophies (85). However, based on the reviewed studies, there was insufficient evidence for the effectiveness of muscle strengthening exercises, although there were some indications that aerobic exercises may have a positive effect on body functions as well as on activities and participation.

There are several limitations to consider when reviewing training studies in muscular dystrophies. First of all, there are only very few randomized controlled trials, each small in sample size. Second, studies are not immediately comparable because they have used training protocols which differ regarding the intensity and duration of the training, targeted muscle groups, type of strength training, i.e. isometric or isokinetic, and type of controls. The majority of exercise training studies have evaluated non-supervised home programs of relatively short duration, using submaximal, low-intensity training levels. The short duration of most strengthening studies does not allow differentiation between neural training effects versus muscle fiber hypertrophy, which generally occurs after six weeks. Third, the compliance of patients, especially during non-supervised home protocols, is a possible confounding factor in all training studies. Fourth, because of the scarcity of patients of each muscular dystrophy, studies have often grouped together several disorders. Persons with different types of muscular dystrophy may however respond very differently to exercise (86). Fifth, some studies used the contralateral non-exercised muscle as a control in muscle strengthening interventions (87-89). The problem with this study design is that there may be confounding cross-over effect in the non-exercised muscles. Moreover, one can hardly expect meaningful

effects of a single-limb training program on a patient's activities, participation and well-being (86). Olsen et al. (90) investigated the effect of aerobic training in 8 patients with FSHD. Twelve weeks of low-intense aerobic exercise improved maximal oxygen uptake and workload with no signs of muscle damage. The authors conclude that aerobic training is a safe method to increase exercise performance in patients with FSHD. Most importantly, only one study described the effect of strength training for experienced fatigue (39) (see section on medication for muscle fatigue and experienced fatigue).

To conclude, aerobic exercise training appears not to be harmful in muscular dystrophies and could have a positive effect on functioning, activities and participation, but the number of high quality studies is low.

MEDICATION FOR MUSCLE FATIGUE AND EXPERIENCED FATIGUE

No curative pharmacological interventions are available, nevertheless, many agents have been proposed as a potential pharmacological treatment for decreasing muscle fatigue in muscular dystrophies. Creatine and β2- agonists have been studied most frequently. Creatine is a well known nutritional supplement among athletes because it increases muscle force and lean body mass (91). Supplementation of creatine monohydrate might enhance muscle performance in patients with muscular dystrophy, as they tend to have lower skeletal muscle creatine levels (see section on pathophysiological studies off muscle fatigue). A recent systematic review on creatine for treating muscle disorders concluded that short- to intermediate-term supplementation with creatine monohydrate in patients with muscular dystrophy may result in a significant, but minimal increase in maximal isometric force of approximately 8.5% in quantitative muscle testing. Most of the potentially clinically relevant effects in muscular dystrophies were seen in dystrophinopathies (92).

Other investigators expected a positive effect of β2- agonists in decreasing muscle fatigue as high doses of β2- agonists have muscle anabolic properties. In animals and healthy volunteers, β2-adrenergic agonists, such as clenbuterol and albuterol, increase muscle strength and muscle mass, in particular when combined with strength training (93, 94). Based on the model by Kalkman et al. (see section on perpetuating factors of experienced fatigue) we might expect that these drugs can decrease experienced fatigue, as many of them are aimed to increase muscle strength. However, in the study by van der Kooi et al., albuterol and a strength training program did not have any effect on experienced fatigue (39). Moreover,

β2- agonists are often associated with numerous undesirable side effects including increased heart rate and muscle tremor, factors that have limited their therapeutical potential. Consequences of prolonged use are presently unclear (38, 39).

Thus, although creatine and albuterol appear to be effective in increasing muscle strength in healthy subjects, they seem to have little effect on muscle strength and experienced fatigue in muscular dystrophies.

COGNITIVE BEHAVIORAL THERAPY

Muscular dystrophies have a large impact on psychosocial functioning as patients must continuously adapt to their progressive illness. Illness cognitions and coping styles influence the level of physical activity and, consequently, experienced fatigue and restrictions in social participation. Hence, changing illness cognitions and coping style may lead to a better quality of life. A cognitive-behavioral approach has been proven successful in the chronic fatigue syndrome (95, 96) and for post cancer fatigue (97, 98) and may be effective in patients with muscular dystrophy as well. Cognitive behavioral therapy in FSHD should, for instance, be focused on the known perpetuating factors of experienced fatigue as described by Kalkman et al., i.e. sleep disturbances, pain complaints and, physical inactivity (66, 99) (see section on perpetuating factors of experienced fatigue). Therapy should be adapted to the life of each individual, resulting in an individualized treatment approach. Altogether, cognitive behavioral therapy seems a rational, promising treatment for fatigue in muscular dystrophies.

Clinical case: treatment of fatigue

Mr A. has never used any drug for alleviating his fatigue. It has simply not been mentioned by any clinician. He believes that physical exercise is beneficial for decreasing his fatigue. In this perspective, he regrets that it is very difficult for him to exercise because of his obesity and poor cardiovascular condition. He is convinced that exercise at a maximum level will lead to overuse. He regards cognitive behavioral therapy as a promising intervention for him.

Clinical case: Experienced fatigue in clinical setting

Mr. A. regrets that his experienced fatigue has never been asked for, nor treated by health workers. He regards his fatigue as an essential disability, whereas his physician has focused on the genetical aspects and diagnosis of the disease. He is happy that fatigue is now on the research and on the medical agenda.

CONCLUSION

Fatigue is not only a frequent, but also a very relevant symptom in patients with muscular dystrophy. Based on the content of this chapter, several recommendations for clinical practice and research can be made. Clinicians should actively ask their patients about the presence of fatigue and its individual characteristics. The nature of the experienced fatigue gives directions to its primary cause. In particular, affective disorders need to be diagnosed or ruled out. The CIS-fatigue questionnaire can be used to measure the severity of experienced fatigue.

The history taking should cover the possible perpetuating factors of fatigue and the perceived disabilities in daily life.

Based on these perpetuating factors, a therapeutic intervention can be proposed. Both in DM and FSHD, specific attention should be paid to sleep disturbances. Specifically in FSHD, the level of physical activity should improve.
Aerobic exercise training appears to be a safe intervention to increase physical activity. It may also be effective in maximizing functional ability and preventing chronic physical complications of inactivity. High-resistance and eccentric strength training should be avoided, particularly in muscular dystrophies caused by defects in structural proteins in the dystrophin-glycoprotein complex, i.e. LGMD, BMD and DMD.

In the future, research on fatigue in muscular dystrophies needs to investigate each type of muscular dystrophy separately, both pathophysiologically and therapeutically. All treatment strategies will ultimately depend on pathophysiology, but the absence of hard evidence should not prevent clinicians and researchers from investigating treatment options based on credible hypotheses.

FIVE KEY PAPERS THAT SHAPED THE TOPIC AREA

Study 1. Wineinger, M.A., Walsh, S.A. and Abresch, T. (2002). Muscle fatigue in animal models of neuromuscular disease. American Journal of Physical Medicine and Rehabilitation, 81, S81-S98.

A review of Wineinger et al. showed that difference in fatigability between dystrophic animal muscles and muscles of healthy animals can largely be explained by differences in muscle fiber types. The dystrophic soleus muscle, which is largely, composed of slow-twitch type I oxidative muscle fibers, fatigued more slowly or at the same rate as that of healthy animals. Yet, the dystrophic extensor digitorum longus (EDL), which has mainly type IIB fibers, was weaker than in healthy animals and generally more fatigable. No differences in fatigability were found between healthy and dystrophic diaphragm muscles. The diaphragm is composed of fast oxidative IIA muscle fibers, which are relatively fatigue resistant (Table 2).

Study 2. Kalkman, J.S., Schillings, M.L., Zwarts, M.J., van Engelen, B.G. and Bleijenberg, G. (2007b). The development of a model of fatigue in neuromuscular disorders: a longitudinal study. Journal of Psychosomatic Research, 62, 571-579.

Kalkman et al. investigated the perpetuating factors of experienced fatigue in patients with FSHD (n = 60) and DM (n = 70) (Figure 2). Only in FSHD, the level of physical (in)activity had a central place in the model. Lower levels of physical activity contributed to higher levels of experienced fatigue and, through that, to restrictions in social participation. The level of physical activity was directly and negatively influenced by loss of muscle strength. In addition, pain complaints influenced levels of experienced fatigue, both directly and indirectly, by decreasing physical activity.

Study 3. Vignos, P.J., and Watkins, M.P. (1966). The effect of exercise in muscular dystrophy. The Journal of the American Medical Association, 197, 843-848.

The first controlled study of strengthening exercise in muscular dystrophies used a regimen with gradual increase in weight resistance in patients with DMD (n=14), FSHD (n=4) and LGMD (n=6) over a one-year period. The authors reported strength improvement throughout the first four months of exercise regardless of type of dystrophy. The degree of improvement was related to the initial strength of the exercised muscle. Therefore, they concluded that exercise programs should begin early in the course of the disease.

Study 4. Florence, J.M. and Hagberg, J.M. (1984). Effect of training on the exercise responses of neuromuscular disease patients. Medicine and Science in Sports and Exercise, 16, 460-465.

Because the hallmark of muscular dystrophy is motor weakness, more studies have been conducted looking at muscle strength training than at aerobic exercise training. Only in 1984, Florence et al. first described a positive effect of aerobic exercise training on the exercise responses of neuromuscular disease patients among which patients with LGMD (n=3) and FSHD (n=1). All patients completed a 12-week cycle ergometry training program, three days per week. The increase in VO2max in the patients was almost the same as that of the healthy subjects (n=4). The authors concluded that patients can develop relatively normal adaptations to training. No definitive deleterious effects of training were demonstrated in these patients.

Study 5. Lindeman, E., Leffers, P., Spaans, F., Drukker, J., Reulen, J., Kerckhoffs, M. and Koke, A. (1995). Strength training in patients with myotonic dystrophy and hereditary motor and sensory neuropathy: a randomized clinical trial. Archives of Physical Medicine and Rehabilitation, 76, 612-620.

The number of recent studies on the effect of training in muscular dystrophy lacking a randomized controlled design is striking. Lindeman et al. first conducted a randomized clinical trial on the effects of strength training in muscular dystrophy. This trial compared the effect of 24 weeks of strength training of the thigh muscles versus no training in 36 adult patients with myotonic dystrophy. The participants trained 3 times a week for 24 weeks with weights adjusted to their force. In the DM patients, none of the outcomes showed any training effect. No serious side effects of the training occurred. Training loads could be gradually increased in all patients, because the repetition maximum improved. Three rather weak DM patients were unable to perform the exercises according to the training instructions. Most of the differences in muscle strength outcomes (isometric, dynamic and endurance) between groups showed small, non-significant positive effects in favor of the training group. Only changes in the endurance measure (13.1 s longer maximum duration of an isometric contraction; 95% CI 2.2 to 24.0) reached statistical significance. No signs of overuse, such as a decline in strength or a rise in parameters of muscle membrane permeability were seen. However, this study imposed merely a controlled strain for a relatively short period.

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Research

CHAPTER 3

184TH ENMC WORKSHOP REPORT: PAIN AND FATIGUE IN
NEUROMUSCULAR DISORDERS

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INTRODUCTION

This European Neuromuscular Centre (ENMC) care workshop was attended by 19 professionals working in the field of neuromuscular disorders (NMD) (pediatric and adult), pain or fatigue from 8 different countries (USA, Great Britain, Germany, France, Italy, Sweden, Denmark and the Netherlands), and 3 patient representatives coming from the Netherlands. This ENMC organized workshop aimed to achieve consensus on the definition of pain and fatigue in NMD, to define a core set of measurement instruments for pain and fatigue in NMD, and to discuss possible interventions. Prior to the workshop, all participants received a questionnaire on the assessment instruments and interventions that they regularly used to, respectively, assess and treat pain and fatigue. Two experts on (chronic) pain and fatigue in general (Henriët van Middendorp and Hans Knoop) were invited to present an overview of definitions, mechanisms, and measurement instruments for pain and fatigue. Next to that, several participants presented data on the prevalence of pain and fatigue in the various NMD populations. Through group discussions with all participants, consensus was reached on the definition and core set of measurement instruments for use in future research and clinical practice in NMD.

BACKGROUND

Pain and fatigue are common symptoms in neuromuscular disorders (NMD) with a prevalence of 30–90%, present in all types of NMD, both in adults and children (1-6). Pain and fatigue have a strong impact on many activities of daily life, including mobility, work, school, leisure, and sleep (4, 7). The differences in reported prevalence could be due to different definitions of pain and fatigue, and various types of measurements. In order to develop effective treatment approaches, both definitions and methods to measure pain and fatigue should be agreed on.

QUESTIONNAIRES

Questionnaires were sent to all participants prior to the workshop to get an overview of the questionnaires on pain and fatigue that are currently used in research and practice in NMD (8). In addition, the various interventions used to treat pain and fatigue were investigated. To assess pain in adults, nearly all participants used the SF-36 (items related to pain), a Likert scale, visual analog scale (=VAS), numeric rating scale (=NRS), and the McGill Pain Questionnaire. For neuropathic pain, more specific scales were mentioned, such as the Douleur Neuropathic 4 (=DN4), Neuropathic Pain Symptom Inventory (=NPSI), or ID-pain. In children, all

used the VAS or the Faces Pain Scale (of which there are many different versions), few used body images to indicate the site of pain or the PedsQol (pain items), and one used the San Salvadour scale for severely handicapped children or the Douleur Enfant Gustav Roussy Scale for children between 2 and 6 years of age.

For fatigue in adults, most of the participants used the Fatigue Severity Scale (=FSS), Borg CR-10 scale, NRS for fatigue, and some used the Modified Fatigue Impact Scale or the Checklist Individual Strength (=CIS). Specific for Myotonic Dystrophy type 1 (DM1), the following sleepiness scales were reported: Daytime Sleepiness Scale (DSS), Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale (ESS), and Unnalinna Narcolepsy Scale (UNS). For children, the (modified) Borg scales were reported and the six minute walking test for ambulant children.

As possible interventions for pain, all participants mentioned guidance and advice for daily activities with special attention for overuse, physical therapy, and possible drugs such as pregabalin, citalopram, duloxetine, amitriptyline, creatine monohydrate, and paminodrate.

For fatigue, possible interventions that were reported included polysomnography to evaluate nocturnal hypoventilation and treatment, guidance and advice for daily activities with special attention for overuse, physical therapy, and cognitive behavioral therapy. Only for DM1 drugs to treat sleepiness were mentioned such as modafinil, citalopram, and Ritalin.

The level of evidence for the efficacy of the interventions is low; available evidence is restricted to drug treatment for neuropathic pain and sleepiness and fatigue in DM (see Cochrane reviews).

PARTICIPANTS' RESEARCH ON PAIN AND FATIGUE IN NMD

Baziel van Engelen reported on several studies in NMD populations, consisting of cross-sectional data of adult DM1 (n = 322), DM type 2 (n = 29), OculoPharyngeal Muscular Dystrophy (OPMD) (n = 35), Chronic Progressive External Ophthalmoplegia (CPEO) (n = 28), Facioscapulohumeral muscular dystrophy (FSHD) (n = 139), and Charcot Marie Tooth (CMT) (n = 137), as well as longitudinal data of adult DM1 (n = 79), FSHD (n = 65), and CMT (n = 73). To assess pain and fatigue in these studies, the McGill pain questionnaire and VAS were used for pain, and the CIS and SF-36 for fatigue. The reported fatigue was between 54% (OPMD) and 68% (CPEO), with significant impact on daily functioning. The pain scores were between 47% (DM1) and 96% (CPEO), with a different distribution pattern for each specific type of NMD. Pain scores were independent of age, impairments, physical activity level, or muscle force. The longitudinal study in FSHD (n = 60) and DM1

(N = 75) resulted in an FSH health status model and a DM1 health status model. Pain and fatigue were main determinants of health status in both diseases (7). These models enable to rationally develop treatment strategies in FSHD and DM1 and form the starting point of the study presented by Nicoline Voet: the protocol of the FACTS-2-FSHD trial. In this recently finished study, aerobic exercise training is compared to cognitive behavioral therapy (data currently in analysis). Pain and fatigue are measured by CIS, VAS for pain, 6 min walking test, and SF36.

Birgit Steffensen reported on a study of self-reported pain and fatigue in patients with FSHD and their healthy relatives or caregivers. The FSS and VAS were used to assess fatigue; pain was measured on a 1–7 scale as adapted from the FSS, by VAS, and by localization on a body image.
Pain and fatigue scores were significantly higher in patients than in healthy persons, there was no statistical difference between patients who were still able to walk and those who were not, and there was a tendency towards higher pain and fatigue scores in patients with less muscle strength.

Marie Kierkegaard reported the results of a cross-sectional study on 70 persons with DM1. The ICF checklist was used for self-rating of perceived pain. Fatigue and excessive daytime sleepiness was evaluated with the FSS and ESS, as well as with the ICF checklist. Fatigue, daytime sleepiness and pain were rated as a problem in 76%, 80% and 51%, respectively. The impact of the cut-off level for fatigue and excessive sleepiness when using the FSS and ESS was stressed. For example, with a score equal or above 4 in FSS 52% are classified as experiencing fatigue compared to 17% when a cut-off score equal or above 5 is used.

Cornelia Kornblum discussed her study of 22 patients with DM1, 22 with DM2, and 22 controls. The FSS, DSS, ESS, PSQI, and UNS were used to assess fatigue and sleepiness as part of a more extensive psychological test set. DM1 showed more sleepiness and fatigue in all measurements compared to the other groups; only the mean KFSS-, DSS-, and PSQI-scores were above the cutoff for pathological performing. The DM2-patients showed more fatigue and a lower sleep quality (mean KFSS- and PSQI-scores were above the cut-off for pathological performing); no differences were found in daytime sleepiness. DM1 and DM2 patients were both more fatigued than healthy controls, and DM1 more than DM2.

Luca Padua showed the results of a study in 392 patients with peripheral nerve diseases, in which the Neuropathic Pain Symptom Inventory (NPSI), VAS, ID-pain, and DN4 were assessed. In 60% of the patients, the VAS-pain was 3 or higher, and approximately 30% had a VAS of 5 or higher. On ID-pain and DN4, 50–60%

had symptoms of neuropathic pain. The NPSI showed no statistical difference between the different symptoms of neuropathic pain, in which paraesthesias had the highest score. In another study on 65 patients with FSHD, the SF-36, VAS-pain, and ID-pain were assessed. According to the ID-pain, 7% of the patients had very probable neuropathic pain, 20% probable neuropathic pain, 24% possible neuropathic pain, 33% no pain, and 16% joint pain exclusively.

Bernard Wuyam showed the preliminary results of an ongoing study on the assessment of neuromuscular dysfunction by means of magnetic nerve stimulation in muscular dystrophies and CMT, and the effect of exercise.

Ulla Werlauff showed results of studies on the perception of pain and fatigue in persons with spinal muscular atrophy (SMA) (52 persons: 7.8–72.6 years) and congenital myopathies (95 persons: 5.5–75.2 years). The PedsQoL (generic, specific), SF-36, Egen classification 2 scale, FSS, and Modified Fatigue Impact Scale were used to measure pain and fatigue. In congenital myopathies, pain was a problem in all muscles (overload?) whereas in SMA-type 2 it was not, or related to an event like surgery.
In this study, fatigue was a problem in congenital myopathies but not in SMA. From her results, Ulla Werlauf concluded that PedsQoL, SF-36 and Modified fatigue impact scale were not very sensitive or conclusive. The recommended scale would be the FSS.

Imelda de Groot showed results of former studies in adults with SMA and ALS and an ongoing study in DMD. In an open questionnaire study in 99 adult SMA patients, divided into two groups (SMA type1–2 and type 3), neck pain was most prevalent in both groups (38% in SMA1-2, and 34% in SMA3); fatigue was reported in 64% in SMA3, in contrast to 34% in SMA1-2. In a study in 74 persons with ALS, no correlations were found between functional abilities (measured with ALS-FRS), and pain or fatigue (measured with SF-36). In the ongoing study in boys with DMD (N = 30) and training, the preliminary results show that boys with DMD have similar adaptations to physical exercise (heart rate and EMG-adaptations) as healthy age-matched controls (N = 99) and comparable subjective fatigue (measured by OMNI scale), but that some boys can perceive/ experience fatigue in rest.

Yaacov Anziska showed preliminary results of two studies: one study in children with NMD (7 with myopathy/limb girdle muscular dystrophy, 9 with DMD, 3 with CMT, and 2 with myasthenia gravis; age range 5– 19 years). The Epworth Sleepiness Scale, the Vignos, and Brooke ratings scales, the Children's Depression Inventory, and the PedsQoL 3.0 Neuromuscular Module for Patients and Parents

were used. Except for the myopathy/DMD-group, there was no correlation between PedsQOL-scores of the patients and those of their parents. There was evidence of mild abnormal mood disorders and mild-moderate sleepiness. A study of 31 adults (5 patients with DM1-2, 14 with LGMD, 5 with CMT, 5 with motor neuron diseases, 2 with myasthenia gravis) in which the SF-36 was used gave similar results.

Carole Bérard showed results of a study in 22 boys with DMD with pain and osteopenia (7 ambulant, and 15 non-ambulant). In 21 of the 22 boys, a moderate to severe pain was measured with NRS, most of the boys (21) experienced pain during physiotherapy; 11 also spontaneously, 9 during the night and 5 (nonambulant) during transfers. There was no correlation between the NRS-pain score and osteopenia.

Anna-Karin Kroksmark shared some practical experiences on pain and fatigue in children with DMD from studies performed at her centre. In these studies, PedsQoL, Multidimensional Fatigue Scale, Sleep Quality Index, and questions about pain and tiredness were used. Pain has an increasing interest in the network in Sweden and a national survey is now being performed. Adapted Faces Scales were shown.

Caron Coleman showed her work on establishing how to measure pain in children: one size does not fit all! Due to the different developmental stages the following measurements were recommended for clinical utility: 0–5 years and cognitive or learning difficulties observation and parent/caretaker report; 5–7 years-faces and questions to child and parents regarding location, frequency, quality (if possible) and impact on function; 8+ years-combination of faces/NRS and questions as above; 13+ years Brief Pain Inventory/faces/NRS.

Heinz Jungbluth gave an overview of different childhood NMD in which exertial myalgia with or without rhabdomyolysis is a common primary or secondary feature. One of the open questions that need to be addressed in future research is whether the different mechanisms underlying these features in distinct disorders will require different treatment approaches.

Marion Main shared some thoughts on pain and fatigue in children with NMD. Pain can be caused by secondary complications of the disorder, such as contractures, cramps, muscle soreness etc. A warning was given that the physiotherapist can be a cause of pain due to treatments like stretching.

She pointed at the lack of knowledge on the topic of fatigue with regard to the role of weakness in the development of fatigue and the important role of exercise in the management of pain and fatigue.

Finally, Jo Auld gave advices on the psychometric properties that outcome measures on pain and fatigue should encompass.

CONCLUSIONS

Pain as well as fatigue are currently measured by various methods and several NMDs have been studied so far. It can be concluded that pain and fatigue are highly prevalent and important problems, both in adults and children. It is important to differentiate pain and fatigue from sleepiness, depression, de-conditioning, and side effects of drugs. Specific types of pain and fatigue, related to the underlying NMD and/or stage of the NMD can be distinguished. These should be differentiated from aspecific pain and fatigue, which are not primary related to NMD.

Fatigue can have physiological features, such as loss of voluntary force or endurance during exercise/activity (both of peripheral and central origin). This type of fatigue is activity-related. This aspect of fatigue is also applicable for cognitive fatigue, defined as a reduction in cognitive performance over time.

PROPOSED DEFINITIONS

As presented by the experts on pain and fatigue, both pain and fatigue are multidimensional concepts and include the following aspects:

- ♦ Characteristics: acute or chronic ("long lasting"), intensity, frequency, location, quality.
- ♦ Cause(s).
- ♦ Consequences or impact on: body function(s), activities of daily life, and participation.
- ♦ Cognitive behavioral factors (predisposing and/or perpetuating).

The proposed definition of pain in NMD is from the International Association of Study on Pain (IASP): pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.

Fatigue can have many definitions. The proposed one is: experienced/subjective fatigue is lack of energy or the existence of weakness or exhaustion – mentally, physically or both.

PROPOSED MEASUREMENT CORE-SETS

Several instruments to measure pain and fatigue in NMD were discussed with experts in the research field (8). Two types of measurement core-sets are proposed: one to use in daily practice and one for research purposes.

For pain the following core-sets are proposed:

Core-set (daily practice):
- ♦ Numeric Rating Scales (faces for children)/Face Legs Activity Cry Consolability (FLACC) in young children.
- ♦ Modified Brief Pain Inventory.
- ♦ Hospital Anxiety and Depression Scale (HADS).
- ♦ Pay attention to organic/biomechanical causes/ neuropathic pain (if the latter is suspected: use ID-pain or DN4).

Research (extended screening):
- Pain Disability Index (PDI) or Brief Pain Inventory (BPI).
- SF-36.
- HADS and/or Beck's Depression Index (BDI).
- Cognitive behavioral factors.
- In case of neuropathic pain, use ID-pain or NPSI.

For fatigue:

Core set (daily practice):
- NRS.
- Checklist Individual Strength (CIS) (norms, multiple dimensions), or if CIS is not available fatigue severity scale (FSS) (impact of fatigue).
- Look for organic/biomechanical causes/forced vital capacity.

Extended/research:
- Physical activity (e.g. actography, activlim).
- Disability scale (e.g. SIP, SF-36).
- Psychological distress (e.g. Hospital Anxiety and Depression Scale).
- Sleep disturbances.
- Social support scale.
- Fatigue-related cognitions.
- Pain.

FUTURE PLANS

This workshop only covers discussions and proposals for definitions of pain and fatigue in NMD and the core set of measurements for daily practice and research. The management of pain and fatigue is still a point to discuss in the future. It was decided to collaborate on the use of the core-sets and share data with each other in order to get more insight in the possible contributing factors of pain and fatigue in NMD. Based on these results, possible management approaches can be discussed in a next workshop on Management of pain and fatigue in NMD.

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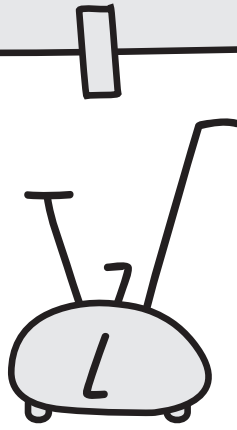
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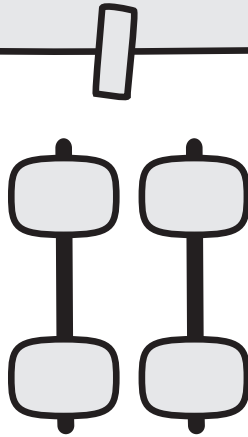
Strength training

CHAPTER 4

STRENGTH TRAINING AND AEROBIC EXERCISE TRAINING FOR
MUSCLE DISEASE

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ABSTRACT

Background
Strength training or aerobic exercise programs might optimize muscle and cardiorespiratory function and prevent additional disuse atrophy and deconditioning in people with a muscle disease. This is an update of a review first published in 2004.

Objectives
To examine the safety and efficacy of strength training and aerobic exercise training in people with a muscle disease.

Search methods
We searched the Cochrane Neuromuscular Disease Group Specialized Register (July 2012), CENTRAL (2012 Issue 3 of 4), MEDLINE (January 1946 to July 2012), EMBASE (January 1974 to July 2012), EMBASE Classic (1947 to 1973) and CINAHL (January 1982 to July 2012).

Selection criteria
Randomized or quasi-randomized controlled trials comparing strength training or aerobic exercise programs, or both, to no training, and lasting at least six weeks, in people with a well-described diagnosis of a muscle disease. We did not use the reporting of specific outcomes as a study selection criterion.

Data collection and analysis
Two authors independently assessed trial quality and extracted the data obtained from the full text-articles and from the original investigators. We collected adverse event data from included studies.

Main results
We included five trials (170 participants). The first trial compared the effect of strength training versus no training in 36 people with myotonic dystrophy. The second trial compared aerobic exercise training versus no training in 14 people with polymyositis and dermatomyositis. The third trial compared strength training versus no training in a factorial trial that also compared albuterol with placebo, in 65 people with facioscapulohumeral muscular dystrophy (FSHD). The fourth trial compared combined strength training and aerobic exercise versus no training in 18 people with mitochondrial myopathy. The fifth trial compared combined strength training and aerobic exercise versus no training in 35 people with myotonic

dystrophy type 1. In both myotonic dystrophy trials and the dermatomyositis and polymyositis trial there were no significant differences between training and non-training groups for primary and secondary outcome measures. The risk of bias of the strength training trial in myotonic dystrophy and the aerobic exercise trial in polymyositis and dermatomyositis was judged as uncertain, and for the combined strength training and aerobic exercise trial, the risk of bias was judged as adequate. In the FSHD trial, for which the risk of bias was judged as adequate, a +1.17 kg difference (95% confidence interval (CI) 0.18 to 2.16) in dynamic strength of elbow flexors in favor of the training group reached statistical significance. In the mitochondrial myopathy trial, there were no significant differences in dynamic strength measures between training and non-training groups. Exercise duration and distance cycled in a submaximal endurance test increased significantly in the training group compared to the control group. The differences in mean time and mean distance cycled till exhaustion between groups were 23.70 min (95% CI 2.63 to 44.77) and 9.70 km (95% CI 1.51 to 17.89), respectively. The risk of bias was judged as uncertain. In all trials, no adverse events were reported.

Authors' conclusions

Moderate-intensity strength training in myotonic dystrophy and FSHD and aerobic exercise training in dermatomyositis and polymyositis and myotonic dystrophy type I appear to do no harm, but there is insufficient evidence to conclude that they offer benefit. In mitochondrial myopathy, aerobic exercise combined with strength training appears to be safe and may be effective in increasing submaximal endurance capacity. Limitations in the design of studies in other muscle diseases prevent more general conclusions in these disorders.

PLAIN LANGUAGE SUMMARY

STRENGTH TRAINING OR COMPREHENSIVE AEROBIC EXERCISE TRAINING FOR MUSCLE DISEASE

Strength training, which is performed to improve muscle strength and muscle endurance, or aerobic exercise programs, which are designed to improve cardiorespiratory endurance, might optimize physical fitness and prevent additional muscle wasting in people with muscle disease. However, people with muscle disease and some clinicians are still afraid of overuse and have a cautious approach to training. This updated review (most recent date of search 2 July 2012) included two eligible trials of strength training in people with facioscapulohumeral

muscular dystrophy (FSHD) and myotonic dystrophy (101 participants), two trials of strength training combined with aerobic exercise in people with mitochondrial myopathy (18 participants) and myotonic dystrophy type I (35 participants) and one trial of aerobic exercise in people with polymyositis and dermatomyositis (14 participants). These trials showed that moderate-intensity strength training in people with myotonic dystrophy or with FSHD, and aerobic exercise training in people with dermatomyositis or polymyositis appear not to harm muscles. Strength training combined with aerobic exercise appears to be safe in myotonic dystrophy type I and may be effective in increasing endurance in people with mitochondrial myopathy. Evidence suggests that strength training is not harmful in people in FSHD, myotonic dystrophy, mitochondrial disorders and dermatomyositis and polymyositis, but further research is needed to determine potential benefit.

BACKGROUND

The term 'muscle disease' comprises a large group of conditions. Skeletal muscles are primarily affected but in some disorders other organ systems may also be involved. Most conditions are progressive, causing the muscles to gradually weaken over time. When a person is diagnosed as having a muscle disease, questions arise about the prognosis, possible interventions and genetics. However, people with muscle disease are usually also concerned about everyday issues such as participation in sports, work and hobbies. We cannot give evidence-based advice about these issues, because we do not know how physical exercise affects the diseased muscular system or the cardiorespiratory system. To answer these questions, controlled trials of aerobic exercise and strength training in people with a muscle disease are needed.

Weakness and impaired cardiorespiratory function are common in people with muscle disease; pain and fatigue may also be common symptoms, all of which contribute to a decreased quality of life. In healthy persons the best intervention to improve strength and cardiorespiratory function is physical training. Strength training or aerobic exercise programs in people with muscle disease might maximise muscle and cardiorespiratory function and prevent additional disuse atrophy (1). However, reports of progression of weakness after exercise in people with myopathies have encouraged a cautious approach to training (2-4). Therefore, many people with a muscle disease were advised to avoid physical exertion (3). Thus the benefit from strength training or aerobic exercise training in muscle diseases is still not clear (5).

The relative rarity of many muscle diseases has led researchers to group participants with different neuromuscular disorders together in one study, including myopathies, neuropathies and motor neuron disease (6-13). As the pathophysiology of these disorders differs, their reaction to an intervention might also be different. Therefore, conclusions about the effect of training derived from these mixed populations cannot readily be extrapolated to people with specific muscular disorders (14).

In this review we systematically analyzed randomized controlled trials (RCTs) of these interventions for people with specified muscle diseases. This review was first published in 2004, with the most recent update of the searches in 2012.

Objectives

To examine the safety and efficacy of strength training and aerobic exercise training in people with a muscle disease.

METHODS

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

We included all RCTs or quasi-RCTs that made any of the following comparisons:
- strength training versus no training;
- aerobic exercise training versus no training;
- combined strength training and aerobic exercise versus no training.

Quasi-RCTs are trials that allocate participants to experimental or control groups based on a method that is not truly random, for example, hospital record number or date of birth.

Types of participants

We selected all trials that included participants with a well-described diagnosis of a muscle disease, such as inflammatory myopathies, metabolic myopathies, muscular dystrophies, muscle diseases with myotonia and other well-defined myopathies. We decided not to include studies looking at strength training or aerobic exercise training for people in whom muscle weakness was not the primary feature, but might have been secondary to chronic renal insufficiency, chronic

heart failure, renal or heart transplantation, or corticosteroid use. We did not review the effects of respiratory muscle training. We did not include studies regarding aerobic exercise training for McArdle disease because there is a separate Cochrane review available for this metabolic myopathy (15). We excluded studies in which participants had a variety of muscle diseases if we could not obtain results for each condition separately. We assessed the diagnostic criteria of each study; diagnosis has to be confirmed by muscle biopsy or genetic testing.

Types of interventions

To date, there is no evidence or recommendation for a minimum duration of training in muscle disease. However, in the first six weeks, the change in muscle strength or aerobic capacity is generally caused by neural adaptation. Therefore, we included all forms of strength training and aerobic exercise training lasting at least six weeks. We excluded all studies using a within-subjects design with the non-exercised limb as a control. If exercises are performed to increase muscle strength on one side of the body, voluntary strength can increase on the contralateral side. This concept is called cross-education, and has been described with different forms of exercises. A meta-analysis of 16 randomized studies concluded that, on average, the magnitude of cross-education is eight per cent of the initial strength of the untrained limb (16). Neural adaptations to training and learning effects due to testing are postulated as explanations (17-20). Moreover, the results may well be confounded by the presence of asymmetric weakness of both limbs, as the absolute gain in muscle strength resulting from strength training is related to pre-exercise muscle weakness (21). For this reason, a non-exercised limb is not an appropriate control, even if training is randomly assigned. For this reason, we have excluded studies using such a within-subjects design.

Definitions

- Training or physical fitness training: a planned, structured regimen of regular physical exercise deliberately performed to improve one or more of the following components of physical fitness: cardiorespiratory fitness, body composition, muscle strength and endurance, and flexibility (22).
- Strength training: a systematic program of exercises designed to increase an individual's ability to exert or resist force using, for example, weights, weight machines or elastic cords (22).
- Aerobic exercise training or cardiorespiratory fitness training: training that is designed to improve the capacity and efficiency of aerobic energy-producing systems and is effective for improving cardiorespiratory endurance. It consists

of an activity or combination of activities that uses large muscle groups, that can be maintained continuously, and is rhythmical and aerobic in nature, for example walking, running, cycling, aerobic dance exercise or swimming (22).

TYPES OF OUTCOME MEASURES

Primary outcomes

The primary outcome measure for strength training was:
- change in muscle strength, expressed in measures of static (that is, isometric) or dynamic strength between baseline and six weeks.

The primary outcome measure for aerobic exercise training was:
- change in aerobic capacity, expressed in measures of work capacity between baseline and six weeks.

Secondary outcomes

The secondary outcome measure specific to strength training was:
- change in muscle endurance muscle endurance or muscle fatigue between baseline and six weeks.

The secondary outcome measure specific to aerobic exercise training was:
- change in aerobic capacity, expressed in measures of oxygen consumption, parameters of cardiac function or parameters of respiratory function between baseline and six weeks.

Secondary outcome measures applicable to both strength training and aerobic exercise training showing a change from baseline and six weeks were:
- timed-scored functional assessments of muscle performance, such as a six-minute walk test (23);
- quality of life measures, such as the Short Form 36 (SF-36) Health Survey (24);
- parameters of muscle membrane permeability (serum creatine kinase level, myoglobin level) to assess safety; pain assessed by an analogue pain scale (25);
- experienced fatigue assessed by questionnaires, e.g. Checklist Individual Strength (CIS-fatigue) (26);
- adverse effects requiring withdrawal of the participant from the study: acute rhabdomyolysis, increasing muscle pain, injury, etc;

We compared data on outcome measures at baseline with those obtained after at least six weeks of training. When there were assessments at more than one time (during the intervention, after cessation of the intervention), our preference was for data on outcome measures obtained at the end of the intervention.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

We searched the following databases: the Cochrane Neuromuscular Disease Group Specialized Register (July 2012), the Cochrane Central Register of Controlled Trials (CENTRAL, in The Cochrane Library 2012, Issue 7 of 12), MEDLINE (January 1946 to July 2012), EMBASE (January 1974 to July 2012), EMBASE Classic (1947 to 1973) and CINAHL (January 1982 to July 2012). We reviewed the bibliographies of the trials identified and other reviews of the subject, and contacted some of the authors in the field to identify additional published and unpublished data.

DATA COLLECTION AND ANALYSIS

Selection of studies

Two review authors (Voet, van der Kooi) checked the references identified by the search strategy. We obtained the full text of all potentially relevant studies for independent assessment by both authors. We decided which trials fitted the inclusion criteria.

Data extraction and management

Two review authors (Voet, van der Kooi) independently extracted the data from the included trials onto a specially designed data extraction form, and graded the risk of bias and certain other aspects of the design of the included trials.

Assessment of risk of bias in included studies

We assessed the risk of bias and other aspects according to the Cochrane approach using the updated guidance in the Cochrane Handbook for Systematic Reviews of Interventions (27).
We assessed the included studies for randomization sequence generation, allocation concealment, blinding (participants and outcome assessors), incomplete outcome data, selective outcome reporting and other sources of bias. When there was uncertainty, we contacted authors for clarification. We resolved disagreements

about fulfillment of inclusion or quality criteria by discussion between the two authors. We made a judgement on each of the 'Risk of bias' criteria, of "High risk of bias", "Low risk of bias" or "Unclear risk of bias". Whenever characteristics of study design or drop-out rates were likely to cause a higher risk of bias, we planned to make a note of this and investigate the possibility of differences in treatment effects varying with the degree of this problem.

Data synthesis

We intended to combine trial results for appropriate pairings of treatments by calculating a mean of the difference between their effects using the Cochrane statistical package Review Manager 5 (RevMan) (28). Because pooling of the results of trials in different muscle diseases is usually not appropriate, we expressed, when possible, the results per muscle disease as mean differences (MDiff) with 95% confidence intervals (CI) for continuous outcomes, and risk ratios (RR) with 95% CI for dichotomous outcome measures. The intended testing for heterogeneity, and consequent actions, turned out to be unnecessary.

Subgroup analysis and investigation of heterogeneity

We decided, in advance, not to perform subgroup analyses based on sex or age because we anticipated that the differences in muscle disease severity would have a much bigger influence on outcome than sex or age. Moreover, the American College of Sports Medicine stated in their Position Stand (22) that relative improvements resulting from aerobic and strength training are similar for young and old, male and female. We presented data for individual muscle diseases separately. As the pathophysiology of each muscle disease differs, we considered that their reaction to training might be different. If in future data are available for meta-analysis, we will consider investigating the effect of different durations of exercise or training intervention.

RESULTS

DESCRIPTION OF STUDIES

In this review, the search retrieved approximately 7400 records. After assessing the titles and abstracts, we identified 61 studies for potential inclusion: 26 completed trials that studied strength training as an intervention, 20 trials studying aerobic

exercise training, and 15 trials studying combined strength training and aerobic exercise, sometimes incorporated in more comprehensive rehabilitation programs. Most strength training trials included people with the following muscle diseases: slowly progressive dystrophies (mostly myotonic dystrophy, limb-girdle dystrophies, facioscapulohumeral muscular dystrophy (FSHD)) and in the older studies, non-specified progressive muscular dystrophies and inflammatory myopathies. Studies on the effects of aerobic exercise training included mainly people with slowly progressive dystrophies and metabolic myopathies (mostly unspecified mitochondrial myopathies).

Studies have generally been limited by small sample sizes. We excluded 48 studies because there was no randomized controlled comparison between training and non-training participants and six studies because of a within-subjects design (see Table 2: Characteristics of excluded studies).

Table 1 Characteristics of included studies

Cejudo 2005	
Methods	Parallel group RCT
Participants	20 adults with mitochondrial myopathy, diagnosed on the basis of clinical, familial and muscle biopsy data
Interventions	Strength training and aerobic exercise training versus no training **Type of training and exercise** Endurance bicycle training, dynamic isotonic with weights **Intensity** Aerobic training: individualized work rate, 30 min leg exercise on an ergo cycle, 70% of the peak work rate; strength training: one set dynamic and isotonic of 10 to 15 repetitions at 50% 1RM load, to 2 or 3 sets. Adjustments on workload changed every 2 weeks **Frequency** 3 times/week **Duration** Session: approximately 60 min. Program: 24 weeks **Muscle groups** Shoulder, upper back, arm, pectoralis major, biceps brachii and brachialis muscles **Supervision** Supervised training program by specialized nurses and a physiatrist specialist in a rehabilitation unit on an outpatient basis
Outcomes	Primary: exercise capacity - expressed in measures of oxygen uptake (ie. VO2 max), endurance time and distance walked in the shuttle walking test. Secondary outcomes were: peripheral muscle strength (1RMtest), quality of life, symptoms of myalgia, cramps and fatigability and functional exercise capacity
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly assigned to a training group or control group" Comment: no published information on the sequence generation. The author (Cejudo) informed us that patients were randomly assigned according to a computer generated randomization list
Allocation conceal-ment (selection bias)	Unclear risk	Quote: "Patients were randomly assigned to a training group or control group" Comment: no published information on the allocation concealment. The author (Cejudo) informed us that patients were randomly assigned according to a computer generated randomization list
Blinding (performance bias and detection bias) All outcomes	High risk	Comment: no published information on the blinding of the outcome assessors and personnel. The author (Cejudo) told us that the evaluators knew to which group each patient was assigned
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "...one patient in each group failed to finish the study for personal reasons" Comment: baseline outcome data assessed, but not available for these patients. So 1/10 missing from intervention group and 1/ 10 missing from control group
Selective reporting (reporting bias)	High risk	No primary and secondary outcome(s) defined in the article
Other bias	Low risk	No risk of bias from other sources detected

Methods	Evaluator blind, parallel group RCT
Participants	35 adults with myotonic dystrophy type 1, genetically confirmed
Interventions	Strength training and aerobic exercise training versus no training **Type of training and exercise** Strength training, aerobic exercise, balance exercises **Intensity** Strength exercises for arm, leg, back and abdominal muscles 16-20 repetitions, for 6- 7 min, balance exercises for 3-4 min, aerobic activities for 11-12 min at 60-80% of maximum heart rate. Once a week a 30-min brisk walk **Frequency** 2 times/week and once a week a brisk walk **Duration** Session: 60 min and a 30-min walk. Program: 14 weeks **Muscle groups** Arm, leg, back and abdominal muscles **Supervision** All sessions were supervised by a specialized physiotherapist
Outcomes	Primary: distance walked in the 6-min walk test Secondary: timed-stands test, timed up-and-go test
Notes	Participants were stratified before randomization by their results in the 6-min walk test

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The lots were drawn by a person who was not involved in any other part of the study"
Allocation concealment (selection bias)	Low risk	Quote: "Patients were randomly assigned to a training group or control group" Comment: no published information on the allocation concealment.
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "Data was collected before and after the intervention by two independent experienced physiotherapists, blinded to group allocation and each assessing the same participants on both occasions"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "one person in the control group did not attend the data collection after the intervention"
Selective reporting (reporting bias)	Low risk	No evidence found for selective reporting
Other bias	Low risk	No risk of bias from other sources detected

Lindeman 1995	
Methods	Evaluator blind, matched-control RCT
Participants	36 adults with myotonic dystrophy (2 congenital form, 34 classical adult type), diagnosis not verified
Interventions	Strength training versus no training **Type of training and exercise** Dynamic strength training with weights **Intensity** Individualized progressive overload, 3 sets from 25 repetitions at 60% of 1RM, via 15 repetitions at 70%, to 10 repetitions at 80% **Frequency** 3 times/week **Duration** Session: within 30 min. Program: 24 weeks **Muscle groups** Knee extensors and flexors, hip extensors and abductors **Supervision** Supervised home training program
Outcomes	Primary: muscle strength by isokinetically measured knee torques and isometrically as MVIC. Main secondary outcomes were: endurance by maximum duration of contraction at 80% of MVIC, functional performance by timed motor performance tests and by questionnaires. Serum myoglobin levels to detect changes in muscle fiber membrane permeability
Notes	Participants were matched based on muscle strength (knee extension torque/bodyweight) and on performance in a stair-climbing test. Only complete pairs were analyzed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Comment: there was no published information on the sequence generation but the author (Lindeman) informed us that 2 independent persons drew a sealed lot per matched pair and allocated it by tossing a coin to the training or non-training group
Allocation concealment (selection bias)	Low risk	Comment: there was no published information on the method of allocation concealment but the author (Lindeman) informed us that 2 independent persons allocated the training, after tossing the coin, to the training or nontraining group

Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "observers of the outcome measurements were blinded for treatment allocation" Comment: approximately 20% of the myotonic dystrophy participants revealed information to the clinical evaluators that resulted in unblinding during the course of the trial
Incomplete outcome data (attrition bias) All outcomes	High risk	3 of the initially 36 randomized participants withdrew before disclosure of treatment allocation. The 33 participants starting the trial made 15 matched pairs. During the trial 1 person dropped out. Because of the matched pair design only complete pairs were analyzed, therefore eventually 28 of the initial 36 randomized participants were analyzed. Follow-up was therefore incomplete and analysis was not by intention-to-treat. However, the flow path of participants was well documented
Selective reporting (reporting bias)	Low risk	No evidence found for selective reporting
Other bias	Low risk	No risk of bias from other sources detected

Van der Kooi 2004	
Methods	Evaluator blind, parallel group, RCT
Participants	65 adults with FSHD, genetically confirmed
Interventions	Strength training versus no training (and as add-on in a double blind randomized controlled design albuterol or placebo) **Type of training and exercise** Dynamic and isometric strength training with weights **Intensity** Individualized progressive overload, 2 sets dynamic from 10 repetitions at 10RM, via 8 repetitions at 8RM, to 5 repetitions at 5RM, and 30s isometric with same weight **Frequency** 3 times/week **Duration** Session: Within 30 min. Program: 52 weeks **Muscle groups** Elbow flexors, ankle dorsiflexors **Supervision** Supervised home training program
Outcomes	Primary: difference in muscle strength of elbow flexors and ankle dorsiflexors after 52 weeks using the MVIC. Main secondary outcomes were muscle endurance (MVIC Force-Time Integral) and dynamic muscle strength (1RM). Other measures included functional tests and timed motor performance tasks

Notes	Outcomes are presented for the 4 treatment groups (i.e. the 4 combinations of training versus non-training, and albuterol versus placebo). Effect sizes are presented by intervention as well	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "...participants were randomly assigned to one of the four treatment groups according to a computer generated randomization list"
Allocation concealment (selection bias)	Unclear risk	Quote: "information on the assignment to training or non-training was disclosed to the participants by the physical therapist"
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "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" Comment: adequate although one of the main secondary outcome measures, the 1RM measurement for assessing dynamic strength, was performed by the physical therapist, who supervised the training, and was therefore not blinded to the allocation to training or non-training. Unblinding during the trial was adequately registered. Allocation to training or non-training was unmasked in 3 cases, due to unintentional remarks
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "One patient stopped training because of recurring, training-related muscle soreness and fatigue. Four participants stopped using their study medication because of side effects. Data for the participants who discontinued an intervention were analyzed in the assigned treatment group" Comment: complete follow-up of all participants
Selective reporting (reporting bias)	Low risk	No evidence found for selective reporting
Other bias	Low risk	No risk of bias from other sources detected

Wiesinger 1998	
Methods	Parallel group RCT
Participants	9 adults with dermatomyositis and 5 adults with polymyositis Diagnosis of primary inflammatory muscle disease was defined by the criteria of Bohan and Peter
Interventions	Aerobic exercise training versus no training **Type of training and exercise** Endurance bicycle training, endurance step aerobics **Intensity** Bicycle training: 30min, slowly increased on an individual basis. Resistance was increased until a heart rate of 60% of maximum. Step aerobics: 30 min **Frequency** During the first 2 weeks, twice weekly, during the remaining 4 weeks, 3 times weekly **Duration** Session: 60 min. Program: 6 weeks **Muscle groups** Not applicable **Supervision** Supervised by a physiotherapist
Outcomes	No primary outcome or secondary outcomes defined. Study outcomes: activities of daily living score, peak isometric torque of knee extensors and hip flexors, peak oxygen consumption and creatine kinase and aldolase levels
Notes	Outcomes are not presented separately for the dermatomyositis and polymyositis patients

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Distinct randomization lists were used". Comment: there was no information about the generation of the list. It is not clear what is meant by "distinct randomization lists"
Allocation concealment (selection bias)	Unclear risk	Comment: there was no published information on the method of allocation concealment
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "Muscle strength assessments were carried out by the same person who was unaware of the group to which the individual patients belonged". Comment: there was no published information about blinding of the assessor of the other measurements
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: complete follow-up of all participants

Selective reporting (reporting bias)	High risk	Comment: no primary or secondary outcomes are defined
Other bias	Low risk	No risk of bias from other sources detected. Outcomes are not presented for dermatomyositis and polymyositis separately

MVIC: maximum voluntary isometric strength, RCT: randomized controlled trial

RM: repetition maximum, VO2 max: maximal oxygen uptake

Only seven studies were RCTs making a comparison between training and non-training participants (7, 14, 29-33). Regrettably, the extension of the initially randomized, controlled six-week aerobic exercise study in people with dermatomyositis and polymyositis by Wiesinger et al (32) lost its randomized controlled design due to a decision of the ethics committee. The randomized controlled strength training combined with aerobic exercise trial which compared eight weeks of walking and strengthening exercises versus no training in 20 participants with different muscle diseases (7) has been excluded as both study groups consisted of participants with various muscle diseases and the outcome measures were not presented for each muscle disease separately. As the pathophysiology of each muscle disease differs, their reaction to training might be different. It is not known if the effect of strength training and aerobic exercise training is the same for every muscle disease. Therefore, data should be presented and analyzed for each disease individually, and the power should be sufficient for each individual disorder. For this reason, no conclusions can be drawn with regard to the effect of exercise training for each specific muscle disease in the trial. Finally, no specific details about the exercise program were provided and the risk of bias of the trial was high.

In conclusion, we included two strength training trials (14, 31), one aerobic exercise trial (33) and two strength training combined with aerobic exercise trials (29, 30) (see Table 1 Characteristics of included studies).

Table 2 Characteristics of excluded studies

Study	Reason for exclusion
Abramson 1952	Not a RCT
Aitkens 1993	Not a RCT. Exercised versus non-exercised control limb (randomly assigned) and patients versus healthy volunteers
Aldehag 2005	Not a RCT
Alexanderson 1999	Pilot study. Not a RCT
Alexanderson 2000	Extension of a pilot study. Not a RCT
Alexanderson 2007	Not a RCT
Arnardottir 2003	Not a RCT
Chung 2007	No non-exercising control group
Dastmalchi 2007	Not a RCT
Dawes 2006	Excluded because of serious insufficiencies in the study design
De Lateur 1979	Not a RCT. Exercised versus non-exercised control limb (randomly assigned)
Escalante 1993	Not a RCT
Florence 1984a	Not a RCT
Florence 1984b	Not a RCT
Fowler 1965	Not a RCT. Exercise combined with medication
Heikkila 2001	Not a RCT. Training program duration of 3 weeks
Hicks 1989	Not a RCT. Training program duration of 1 month
Hoberman 1955	Not a RCT. 3 drugs added to a comprehensive regimen of therapies, including breathing and resistive exercises
Jeppesen 2006	Not a RCT
Jeppesen 2009a	Not a RCT
Johnson 2007	Not a RCT
Johnson 2009	Not a RCT
Kelm 2001	Not a RCT
Kilmer 1994	Not a RCT. Exercised versus non-exercised control limb (randomly assigned) and patients versus healthy volunteers
Kilmer 2005	Not a RCT. Training program duration for participants with muscle disorders ranged from approximately 1 to 21 months
Lenman 1959	Not a RCT. Training program duration for participants with muscle disorders ranged from approximately 1 to 21 months
Mate-Munoz 2007	Not a RCT
McCartney 1988	Not a RCT. Exercised versus non-exercised control limb (randomly assigned)

Mielke 1990	Not a RCT
Milner-Brown 1988a	Not a RCT. Training program duration for participants with muscle disorders ranged from approximately 2 to 48 months
Milner-Brown 1988b	Not a RCT. Intervention is not training versus non-training, but training added to electric stimulation or electric stimulation only in 1 limb versus a non-stimulated, non-exercised control limb
Milner-Brown 1990	Not a RCT. Intervention is not training versus no training, but amitriptyline added to strength training
Murphy 2008	Not a RCT
Na 1996	Not a RCT. Intervention is not training versus non-training, but training and daily quinine sulfate
Nader 2010	Not a RCT
Olsen 2005	Not a RCT
Omori 2010	Not a RCT
Orngreen 2005	Not a RCT
Scott 1981	A RCT that makes a comparison between 2 different training regimes. No comparison of training versus non-training participants
Siciliano 2000	Not a RCT
Spector 1997	Not a RCT
Sunnerhagen 2004	Not a RCT
Sveen 2007	Not a RCT
Sveen 2008	Not a RCT
Taivassalo 1998	Not a RCT
Taivassalo 1999	Not a RCT
Taivassalo 2001	Not a RCT
Taivassalo 2006	Not a RCT
Tollbäck 1999	Not a RCT. Exercised versus non-exercised control limb (randomly assigned)
Trenell 2006	Not a RCT
Varju 2003	Not a RCT. Training program duration of 3 weeks
Vignos 1966	Not a RCT
Wiesinger 1998b	A non-randomized extension of a RCT (Wiesinger 1998a)
Wright 1996	Not a RCT
Yildirim 2007	Not a RCT

RCT: randomized controlled trial

The first strength training trial compared the effect of 24 weeks of training versus no training in 36 adults with myotonic dystrophy and 30 adults with hereditary motor and sensory neuropathy types I or II (14). As this review is concerned with muscle disease, we will not discuss the results of the hereditary motor and sensory neuropathy participant group. The aerobic exercise trial compared six weeks of cycle and step aerobics exercise with no training in nine adults with dermatomyositis and five adults with polymyositis (33). The second strength training trial compared 52 weeks of strength training versus no training in a factorial trial that also compared albuterol with placebo after the first 26 weeks of training in 65 adult participants with FSHD (30). Only the results for the comparison strength training versus no training will be discussed in this review. The first combined aerobic exercise and strength training trial compared 12 weeks of cycle exercises and dynamic and isokinetic strength training versus no training in 18 people with mitochondrial myopathy (29) (see Table 1 Characteristics of included studies). The second combined aerobic exercise and strength training trial compared 14 weeks of balance exercises, aerobic activities, flexibility exercises, strength exercises and a brisk walk versus no training in 35 people with myotonic dystrophy type I. (30).

RISK OF BIAS IN INCLUDED STUDIES

Strength training trial in myotonic dystrophy

In the first myotonic dystrophy trial (14), participants with myotonic dystrophy were individually matched for muscle strength and performance in a stair-climbing test. Within each matched pair, participants were randomly assigned to the training or control group.
There was no published information on the method of randomization or on allocation concealment but the first author (Lindeman) informed us that two independent persons drew one sealed name per matched pair and allocated it to the training or non-training group by tossing a coin. We graded the intention to blind the clinical evaluators as adequate, although approximately 20% of the myotonic dystrophy participants revealed information to the clinical evaluators that resulted in unblinding during the course of the trial. The authors considered the baseline comparability of the groups as suboptimal because the training group had longer time scores for stair climbing (a measure of functional ability) and had higher knee torques (a measure of muscle strength). They argued that the first three items could have resulted in an underestimation of the training effect, whereas the last item could have resulted in an overestimation of the training effect. They concluded that the differences in experimental group composition did not seem to explain the absence of differences in outcomes between treatment groups. We considered the

way the authors presented and discussed the baseline differences as adequate. Three of the initially 36 randomized participants withdrew before disclosure of treatment allocation. The 33 participants starting the trial made 15 matched pairs. During the trial one person dropped out because of knee problems. Because of the matched pair design only complete pairs were analyzed, thus eventually 28 of the initial 36 randomized participants were analyzed. Follow-up was therefore incomplete and analysis was not by intention-to-treat. However, the flow path of participants was well documented.

Dermatomyositis and polymyositis trial

In the dermatomyositis and polymyositis trial (33), nine people with dermatomyositis and five with polymyositis were randomly assigned to the training or control group using distinct randomization lists. The training group received six weeks of bicycle exercises and step aerobics. Participants in the control group did not undergo any training and continued their previous way of life. There was no published information on allocation concealment and our attempts to obtain further information on this were not successful. During the strength measurements, the clinical evaluator was blinded to the treatment allocation. The success of blinding of assessors was not formally checked as blinding of participants is not possible in an exercise study. There was no published information on blinding during the other measurements. Baseline characteristics were presented for both groups. The authors considered the two groups to be well balanced with respect to most baseline characteristics. There was complete follow-up of all participants.

Facioscapulohumeral muscular dystrophy (FSHD)

In the FSHD trial (31), 65 participants were stratified into two groups based on muscle strength. Participants in both strata were randomly assigned to one of the four treatment groups according to a computer-generated randomization list. The treatments consisted of training plus albuterol, training plus placebo, non-training plus albuterol, or non-training plus placebo. Training or non-training was the first intervention, starting just after the baseline visit until after the final visit at 52 weeks. Information on the assignment to training or non-training was disclosed to the participants by the physical therapist (supervising the training program) after their baseline visit. The clinical evaluator was blinded for the assignment to both interventions. The participants, physical therapist and the neurologist evaluating side effects were blinded to the treatment allocation. The blinding of the clinical evaluator was considered adequate, although one of the main secondary outcome measures, the one-repetition maximum (1RM) measurement for assessing dynamic

strength, was performed by the physical therapist who supervised the training, and who was therefore not blinded to the allocation to training or non-training. Allocation to the training or non-training group was unmasked in three cases, due to unintentional remarks. The success of blinding was not formally checked. Baseline characteristics were presented for all treatment groups. One participant stopped training but still attended all trial visits, resulting in complete follow-up of all participants. Data analysis was by the intention-to-treat principle. As no statistically significant interactions between the two interventions (that is, training versus non-training) could be detected, the effect sizes, being the differences in mean change from baseline, were presented for each intervention. In the mitochondrial myopathy trial (29), 20 participants were randomly assigned to the training or control group. There was no published information on the method of randomization, allocation concealment, or blinding of the evaluators. The author (Cejudo) informed us that participants were randomly assigned according to a computer generated randomization list. The evaluators were not blinded to the intervention allocation, but knew to which group each participant was assigned. One participant in each group failed to finish the study for personal reasons. Baseline characteristics were presented for both groups, except for the participants lost to follow-up. Follow-up was therefore incomplete and analysis was not done by intention-to-treat. No flow path of participants was documented. The authors considered both groups as comparable with respect to age and gender, as well as to each measured variable at baseline.

Combined aerobic exercise and strength training trial in myotonic dystrophy type 1

In the second myotonic dystrophy trial (30), the median value of the results of the six-minute walk test was used to divide the 35 participants into two strata from which they were divided into the training or the control group. The lots consisted of folded pieces of paper with the name of the participant and were drawn by a person not involved in any part of the study. Since participants were recruited before randomization, concealed allocation procedures were applied. An intention-to-treat analysis was applied. Three participants had missing data for perceived exertion at baseline and one person in the control group did not attend the measurement after the intervention but still completed the questionnaires. There was no significant difference in sex or age of participants between groups in the study; however, the mean muscular impairment scale (MIRS) grade was higher in the exercise group, indicating that participants in the exercise group were more severely impaired than participants in the control group. The training group received a comprehensive group exercise training program, they were also asked

to perform an active 30min walk every week. The participants in the control group were advised to live their normal lives and to maintain their degree of physical activity during the study period.

The degree of activity of both groups was not objectively checked.

We ranked each criterion using the Cochrane 'Risk of bias' tool. The review authors' judgements about each risk of bias item for included studies are presented in Figure 1.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias and detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Otzer bias
Cejudo 2005	+	?	-	-	-	+
Kierkegaard 2011	+	+	+	+	+	+
Lindeman 1995	+	+	+	-	+	+
Van der Kooi 2004	+	?	+	+	+	+
Wiesinger 1998	?	?	?	+	-	+

Figure 1 Risk of bias summary: review authors' judgements about each risk of bias item for each included study

QUALITY OF DIAGNOSTIC CRITERIA

This assessment took into account if and how diagnoses were verified. In the first myotonic dystrophy trial (14), participants were recruited via neurologists, physiatrists and the Dutch association for neuromuscular diseases (Vereniging Spierziekten Nederland) on clinical grounds and without genetic verification. We therefore considered the quality of the diagnostic criteria as inadequate. In the second myotonic dystrophy (type I) trial (30), the diagnosis was genetically confirmed in all participants and the diagnostic criteria are therefore adequate. In the dermatomyositis and polymyositis trial (33), all the participants had an established diagnosis of primary inflammatory muscle disease as defined by the established criteria of Bohan and Peter, with a disease duration of at least six months (34, 35). In all participants, muscle biopsies, electromyograms and

laboratory studies had been performed to establish the diagnosis. We therefore considered the quality of the diagnostic criteria to be adequate.

In the FSHD trial (31), participants or a first-degree relative had the associated deletion at chromosome 4 (36). The quality of the diagnosis was therefore adequate. In the mitochondrial myopathy trial (29) participants were recruited from a larger group of patients followed at the university hospital of Sevilla, Spain. Diagnosis was based on clinical and muscle biopsy data. Biopsy findings were determined by biochemical and histological techniques without genetic verification. One participant in each group had only a probable diagnosis of mitochondrial myopathy. The quality of the diagnostic criteria is therefore uncertain.

QUALITY OF TRAINING PROGRAM

The training programs of the first myotonic dystrophy (14), FSHD (31), mitochondrial myopathy (37) and dermatomyositis and polymyositis (33) trials fulfilled most of the minimum requirements as defined by the American College of Sports Medicine (ACSM) Position Stand (22). In the second myotonic dystrophy type I trial (30), the intervention consisted of a comprehensive group exercise training program supported by music. The author could not give the exact training load of each strength training exercise as a percentage of repetition maximum (RM) as it was not tested that way. However, all major muscle groups were trained: arm, back, leg and abdominal muscles (30). The training scheme for the other strength training trials was inadequate only with respect to the number of muscle groups trained, as the ACSM recommends eight to 10 exercises of all the major muscle groups. Only four muscle groups were trained in the first myotonic dystrophy trial (14), two in the FSHD trial (31) and three in the mitochondrial myopathy trial (29). All studies except the combined aerobic exercise and strength training in myotonic dystrophy type I trial (30), focused on a limited number of muscle groups for reasons of effect evaluation, safety and time restraints per training session. In the dermatomyositis and polymyositis trial (33), the training frequency was only twice a week in the first two weeks, but increased to three times a week in the remaining four weeks. In the mitochondrial myopathy trial (29), there was no published information regarding supervision.
In the other trials (14, 30, 31), a physiotherapist supervised training. A description of the training programs is given in the Characteristics of included studies (Table 1).

Table 3 Summary of findings for the main comparison

Strength training compared to usual care for facioscapulohumeral muscular dystrophy					

Patient or population: facioscapulohumeral muscular dystrophy
Settings: at home
Intervention: strength training
Comparison: usual care

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	**Corresponding risk**				
	Usual care	Strength training				
Difference in dynamic muscle strength of elbow flexors	The mean difference in dynamic muscle strength of elbow flexors in the control groups was **1.39 Nm**	The mean difference in dynamic muscle strength of elbow flexors in the intervention groups was **1.17 higher** (0.18 to 2.16 higher)		65 (1 study)	●●● **moderate[1]**	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] The lower confidence limit crosses the minimal important difference.

Table 4 Additional summary of findings

Aerobic exercise and strength training compared to usual care for mitochondrial myopathy

Patient or population: mitochondrial myopathy
Settings: unclear
Intervention: aerobic exercise and strength training
Comparison: usual care

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	**Corresponding risk**				
	Usual care	**Strength training**				
Difference in work capacity - mean time until exhaustion in cycle test electronically braked ergo cycle Follow-up: mean 12 weeks	The mean difference in work capacity - mean time until exhaustion in cycle test in the control groups was **-2.7 min**	The mean difference in work capacity - mean time until exhaustion in cycle test in the intervention groups was **23.7 higher** (2.63 to 44.77 higher)		18 (1 study)	●●● **moderate[1]**	
Difference in work capacity - mean time until exhaustion in cycle test electronically braked ergo cycle Follow-up: mean 12 weeks	The mean difference in work capacity- mean distance until exhaustion in cycle test in the control groups was **-0.9 km**	The mean difference in work capacity- mean distance until exhaustion in cycle test in the intervention groups was **9.7 higher** (1.51 to 17.89 higher)		18 (1 study)	●●● **moderate[1]**	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

[1] In this trial, clinical evaluators were not blinded, which may have led to an overestimation of the training effect on muscle strength and aerobic capacity. Analysis in this trial was not by intention-to-treat.

EFFECTS OF INTERVENTIONS

See: Summary of findings for the main comparison (Table 3); Strength training compared to usual care for facioscapulohumeral muscular dystrophy; Additional Summary of findings 2 (Table 4). Aerobic exercise and strength training compared to usual care for mitochondrial myopathy. We intended to combine trial results for appropriate pairings of treatments by calculating a mean of the difference between their effects using the Cochrane statistical package RevMan. Because we could not obtain the original data for the mitochondrial myopathy (29), dermatomyositis and polymyositis (33) and myotonic dystrophy trials, we describe the results of these trials as published in the article. We were unable to produce MDiffs and 95% CIs for the myotonic dystrophy trial (14) because of the matched pair design. We report the findings of the study as given in the paper.

Primary outcome measure for strength training: muscle strength, expressed in measures of static (i.e. isometric) or dynamic strength

Muscle strength was the primary outcome measure for the first myotonic dystrophy (14) and FSHD trials (31). In the first myotonic dystrophy trial (14), differences in muscle strength were measured isokinetically on a dynamometer as maximum concentric knee torques at three velocities, and isometrically as maximum voluntary contraction. Knee torques of the myotonic dystrophy group did not show any statistically significant difference between the training and control groups, as found with a paired t-test. After 24 weeks, mean change in isokinetic knee torque extension was 1.4 Nm (SD 8.2) for the control group and 5.3 Nm (SD 12.9) for the training group, p = 0.34. Mean change in isokinetic knee torque flexion was 3.7 Nm (SD 8.6) for the control group and 7.4 (SD 11.4) for the training group, p = 0.34 and mean change in maximum isometric voluntary contraction was 6.6 Nm (SD 11.0) for the control group and 8.7 Nm (SD 14.71) for the training group, p = 0.67.
The primary outcome measure in the FSHD trial (31) was a change in maximum voluntary isometric strength of the elbow flexors and ankle dorsiflexors, measured on a Quantitative Muscle Assessment fixed myometry testing system. After 52 weeks the isometric strength of the elbow flexors did not differ significantly between the training and non-training group, for the right side the difference in the means was 0.54 kgF (95% CI - 0.38 to 1.46), with the better score being for the training group. Dynamic strength was evaluated using the one repetition maximum (1RM), the weight a person can lift once, but not twice, at a steady controlled pace through the full range of joint motion. The 1RM of the elbow flexors showed a significantly larger increase in the training group compared to the non-training group (for the right side the difference in the means was 1.17 kg (95% CI 0.18 to

2.16). Both strength measures of the ankle dorsiflexors decreased significantly and markedly in all treatment groups. This decrease was not influenced by training (on the right side the difference in the means in maximum voluntary isometric contraction (MVIC) was 0.43 kgF (95% CI -1.62 to 2.48) more for the training group, in 1RM the difference was -0.44 kg (95% CI -1.77 to 0.89) less for the training group). Differences between groups for the left sided trained muscles did not materially differ from those for the right side.

Muscle strength was a secondary outcome in the mitochondrial myopathy trial (29). In this trial, weight-lifting capacity was measured as the heaviest weight that could be lifted throughout the complete range of movement (1RM test). After the study period, all participants showed increases in all 1RM tests. After 12 weeks, weight-lifting capacity did not differ significantly between the training and non-training group. The differences in mean 1RM between groups were -5.00 kg (95% CI -14.71 to 4.71) less for the training group for the shoulder press exercise, 6.40 kg (95% CI -2.89 to 15.69) in favor of the training group for the butterfly exercise and 7.30 kg (95% CI -2.91 to 17.51) in favor of the training group for the biceps curls exercise.

Primary outcome measure for aerobic exercise training: aerobic capacity, expressed in measures of work capacity

This outcome was published in the mitochondrial myopathy trial (29) and was a primary outcome in the combined aerobic exercise and strength training trial in myotonic dystrophy (30).

In the inflammatory muscle disease trial (33), no primary outcome measure was defined and aerobic capacity was not measured.

In the mitochondrial myopathy trial (29), work capacity was measured in a cycle test and in the shuttle walking test. Endurance time was measured in a submaximal cycling test at a constant workload of 70% of the maximum power output achieved during the baseline incremental cycle test. After 12 weeks, the differences in mean time and distance cycled till exhaustion and leg fatigue or breathlessness exhaustion differed significantly between groups. The differences in mean time and distance cycled till exhaustion between groups were 23.70 min (95% CI 2.63 to 44.77) and 9.70 km (95% CI 1.51 to 17.89), respectively. The distance walked until exhaustion was measured in the shuttle walking test and was 78.00 m more for the training group (95%CI -144.86 to 300.86). The primary outcome in the second myotonic dystrophy type I trial (30) was the distance walked in the six-minute walk test. A difference above or equal to 6% in distance walked between the baseline

measurement and the measurement after the intervention period of 14 weeks was considered as a minimally clinically important change. After 14 weeks, the differences in mean distance walked in the six-minute walk test was 11.00 m (95% CI -66.92 to 88.92), in favor of the training group.

Secondary outcome measures for aerobic exercise or strength training, or both Aerobic capacity, expressed in measures of oxygen uptake (i.e. VO2 max)

This outcome was available for the mitochondrial myopathy (29) and inflammatory muscle disease trial (33). In the inflammatory muscle disease trial (33), work capacity was measured during an incremental cycle test on a cycle ergometer. Maximal oxygen uptake (VO2max) was defined as the highest O2 consumption obtained during the symptom-limited exercise test. After six weeks, the difference in mean VO2 max (ml/ min/kg) was 14.6% higher for the training group (95% CI -0.96 to 30.16). In the mitochondrial myopathy trial (29), VO2 max was noninvasively determined in a maximal incremental cycle exercise test. After 12 weeks, the difference in mean VO2 max was 400 ml/ min (95% CI 61.97 to 861.97) in favor of the training group.

Muscle strength, expressed in measures of endurance or fatigue

This outcome was published for the first myotonic dystrophy (14) and FSHD (31) studies. In the myotonic dystrophy trial (14) endurance was measured as maximum duration of contraction at 80%ofMVIC on an isokinetic dynamometer. After 24 weeks, the difference in MVIC for the control group was -7.4 s (SD 12.0) and for the training group 5.7 s (SD 17.0), p = 0.09. This difference was mainly due to a decrease in endurance in the non-training group.
In the FSHD trial (31), muscle endurance was expressed as a Force-Time Integral (FTI30) of a sustained 30 s maximal isometric contraction measured on a Quantitative Muscle Assessment fixed myometry testing system. After 52 weeks, the FTI30 of the elbow flexors did not differ significantly between the training and non-training group. The FTI30 of the ankle dorsiflexors decreased significantly and markedly in all treatment groups. This decrease was not influenced by training (for the right side the difference in the means was -1 kgF.s (95% CI -42 to 41). Changes in FTI30 for the left-sided trained muscle groups did not differ significantly from the right-sided results.

(Time-scored) functional assessments of muscle performance

This outcome was available for all trials (14, 30, 31, 33) except the mitochondrial myopathy trial (29). In the first myotonic dystrophy trial (14), functional assessments comprised the following time-scored activities: ascending and descending stairs, rising from a chair, rising from supine, walking 50 m as fast as possible, and walking 6 m at natural speed. In the inflammatory muscle disease trial (33), the modified Functional Assessment Screening Questionnaire was used for evaluating disability (38).

In the FSHD trial (31) the functional tests consisted of the assessment of a functional upper extremity grade and functional lower extremity grade (39), and the following timed-scored tasks: standing from lying supine, standing from sitting, walking 30 feet (9.14 m), and climbing three standard stairs (39). In the combined aerobic exercise and strength training trial in myotonic dystrophy type 1 (30), the timed-stands test, and the timed up-and-go test were used for evaluation of effects of the exercises.

In all trials (14, 30, 31, 33), no differences between groups in functional assessments were reported.

Quality of life

This outcome was assessed in the FSHD trial (31) using the Sickness Impact Profile (SIP) and the Symptom-Checklist (SCL-90-R). The mean total of the SIP and its subscales did not demonstrate relevant or significant changes for either the training or non-training groups. In addition, for both groups the mean SCL total did not change between the baseline and final visit.

In the mitochondrial myopathy trial (29), the Nottingham Health Profile (NHP) questionnaire was used. Scores ranged from 0 (no problem) to 100 (maximum problem). The MDiff in overall mean score between both groups was -9.80 (95%CI -25.70 to 6.14).

In the aerobic exercise and strength training trial in myotonic dystrophy type I (30), quality of life was measured by the SF-36 Health Survey. The scores on all subscales of the SF- 36 did not demonstrate relevant or significant changes for either the training or non-training group.

Parameters of muscle membrane permeability (serum creatine kinase level, serum myoglobin level, serum aldolase level)

This outcome was available for the first myotonic dystrophy trial (14), mitochondrial myopathy trial (29) and inflammatory muscle disease trial (33). In the myotonic dystrophy trial (14), serum myoglobin levels were assessed just before and one hour after the measurement session at the baseline visit and at the final visit. Changes in serum myoglobin activity one hour after a standardised test should reflect changes in muscle fiber permeability due to muscle damage. The mean rise in serum myoglobin levels did not differ significantly between the training and the non-training group (-21.00 ng/l, 95% CI -48.35 to 6.35). In the inflammatory muscle disease trial (33), serum levels of creatine kinase and aldolase were measured weekly on Monday after a weekend recovery phase without exercise. There was no statistically significant change in serum creatine kinase level and serum aldolase level during the observation period either in the control group (mean - 13.9%, 95% CI -41.34 to 13.54) or in the training group (mean -6%, 95% CI -22.66 to 10.66).

In the mitochondrial myopathy trial (29), the authors state that the participants' serum creatine kinase levels remained unaltered after the intervention period. However, data for the serum creatine kinase level were not published. In the FSHD trial (31), one participant stopped training because of recurring, training-related muscle soreness and fatigue. A diagnostic work-up revealed a mitochondrial myopathy as well as FSHD. In the mitochondrial myopathy trial (29), cancellations of exercise sessions by participants happened because of muscle soreness associated with the exercise activity. However, every participant was able to tolerate the exercise training regimen without complications. In the first myotonic dystrophy trial (14), a few participants complained of muscle soreness and transient strength reduction after eight weeks. However, no signs of muscle damage were found at the final visit after 24 weeks. In the second myotonic dystrophy trial (30), one person had periods of atrial arrhythmia; however, this was not in connection with the training and the participant was allowed to complete the study by a cardiologist. No other adverse effects were reported. In all trials no other signs of overuse, such as a decline in strength measures (14, 29, 31) or training-related increase in pain or fatigue (31) were reported.

Pain

This outcome was available in both the FSHD (31) and mitochondrial myopathy trials (29). In the FSHD trial (31), 11 out of 34 participants in the training group

reported pain in the neck and shoulder region to the physical therapist during home visits. Five people mentioned a period with elbow complaints. However, the number of people with neck-shoulder and elbow complaints did not differ between treatment groups at baseline nor at the final visit. Moreover, the number of participants with neck-shoulder and elbow complaints slightly decreased in both groups. RR at the final visit was 1.02 (95%CI 0.66 to 1.58) for neck-shoulder and 1.82 (95%CI 0.17 to 19.13) for elbow complaints in favor of the non-training group. Although not formally quantified, the authors mentioned that participants experienced no notable muscle soreness after training.

At the final visit, scores on the VAS for pain and the mean daily rated pain scores did not demonstrate significant changes for either group.

In the mitochondrial myopathy trial (29), participants' arm and leg myalgia was recorded by a simple questionnaire and scored as mild, moderate or severe. Two people in the exercise group and three people in the control group reported severe myalgia in arms and legs. Seven people in the exercise group and five people in the control group reported moderate myalgia in arms and legs. After the 12-week training program no participants in the exercise group and five participants in the control group still reported symptoms of myalgia.

Experienced fatigue

In the FSHD trial (31), experienced fatigue was measured by the subscale "fatigue severity" of the Checklist Individual Strength (CIS-fatigue). At the final visit, the mean score on the CIS-fatigue did not change significantly between the baseline and final visit for either group. The mean daily rated fatigue score of the participants in the training group slightly decreased, whereas the score in the non-training group showed a small increase.

In the mitochondrial myopathy trial (29), participants' usual fatigability was recorded in a simple questionnaire and scored as mild, moderate or severe. Three participants in the exercise group and five participants in the control group reported severe fatigue in arms and legs. At the end of the study period, no participants in the exercise group and five participants in the control group reported severe fatigue in arms and legs. Six participants in the exercise group and two participants in the control group reported moderate fatigue. After the intervention period, five participants in the exercise group and two participants in the control group still reported moderate fatigue.

Adverse events

There were no serious adverse effects related to strength or aerobic training.

DISCUSSION

Only six out of the 60 identified studies on the effect of training in people with muscle disease used a randomized controlled design (7, 14, 29-31, 33). The randomized controlled strength training combined with aerobic exercise trial which compared eight weeks of walking and strengthening exercises versus no training in 20 participants with different muscle diseases (7) has been excluded because the outcome measures were not presented separately for each different muscle disease. Moreover, no specific details about the exercise program were provided and the risk of bias of the trial was judged as 'high'.

The strength training trial in FSHD participants (31) had minor methodological shortcomings. One of the main secondary outcome measures, the 1RM strength measurement, was performed by a physical therapist not blinded to the allocation to training or non-training. The overall risk of bias was, therefore, judged as 'low'.

The dermatomyositis and polymyositis trial (33) had several uncertainties regarding the generation of the randomization list, allocation concealment and blinding of the assessor. No primary or secondary outcome measures were defined. The overall risk of bias was, therefore, judged as 'unclear'. In the myotonic dystrophy strength training trial (14) diagnoses were not adequately verified. Furthermore, analysis was not by intention-to-treat partly due to the matched-pair design. Because of these major methodological shortcomings, we judged the overall risk of bias as 'unclear'.

In the mitochondrial myopathy trial (29), clinical evaluators were not blinded, which may have led to an overestimation of the training effect on muscle strength and aerobic capacity. Analysis in this trial was not by intention-to-treat. The overall risk of bias was therefore judged as 'unclear'. Most differences in mean muscle strength outcomes (isometric, dynamic and endurance) between groups in all trials showed small, non-significant beneficial effects in favur of the training groups. In the first myotonic dystrophy trial (14), only changes in the endurance measure (13.10 s longer maximum duration of an isometric contraction (95%CI 2.20 to 24.00)) and in the FSHD trial (31) only the dynamic strength measure for the elbow flexors (concentric contraction with 1.20 kg heavier weight (95% CI 0.18 to 2.16)) reached statistical significance. However, no adjustments were made for multiple comparisons.

The absent or limited positive effects of strength training on muscle strength could reflect the inability of the diseased muscular system to respond with normal neural and trophic adaptations to the applied training stimuli. However, part of this lack of response could be due to the specificity of the training (14). All adaptations to training are specific to the stimuli applied. Specific strength training essentially involves exercising the muscles in the same manner as the expected use (40). This means that a training program with dynamic exercises increases dynamic strength more than isometric strength, and vice versa. This phenomenon of specificity of training has implications for the sensitivity of the outcome measures; for example, the positive effect of a dynamic strength training program may be captured by using a dynamic evaluation technique, but might be missed using an isometric strength measure. The size of the carry-over effect from, for example, dynamic strength to isometric strength cannot be predicted and it may be that there is a diminished ability of the diseased muscular system to transfer effects of a specific training program from one strength modality to another (31).

In the FSHD trial (31), training did not influence strength of the ankle dorsiflexors, in contrast to the elbow flexors.
The authors thought that a difference in grade of muscle weakness at baseline between elbow and ankle dorsiflexors might provide the explanation for the difference in their response to training. In this study elbow flexors were eligible for testing and training when strength according to the MRC scale grade was three or more, whereas ankle dorsiflexors were eligible when the muscles moved the ankle joint in a position between dorsiflexion and plantarflexion, which potentially includes MRC grades less than three (41). Therefore, pre-exercise weakness might have been more severe in ankle dorsiflexors compared to elbow flexors. In people with a muscle disease, it is assumed that absolute gain in muscle strength resulting from strength training is probably related to pre-exercise muscle strength, and that severely weakened muscles (< 10% of normal strength) may not be able to improve. However, this widely reported assumption is based on one published observation only (12).

In the mitochondrial myopathy trial (29), the MDiff in aerobic capacity as measured in a submaximal cycle test differed significantly between the training and non-training group after the study period. Participants in the training group cycled on average 23.70 min (95% CI 2.63 to 44.77) and 9.70 km longer (95% CI 1.51 to 17.89) than participants in the control group. The distance walked in the shuttle walking test did not differ between groups. This could be explained by the specificity of training, because training consisted of cycling rather than walking exercises.

The timed-scored functional assessments did not demonstrate any relevant or significant changes between treatment groups in the two myotonic dystrophy trials (14, 30), the dermatomyositis and polymyositis trial (33) or the FSHD trial (31). This may be due to the small number of muscle groups trained, the absent or limited effects on muscle strength, and the specificity of the training stimuli applied. In all trials no signs of overuse were reported. This is of major clinical importance because these findings do not support the notion of increased risk of muscle strain in slowly progressive muscular dystrophies. However, adverse events were only mentioned in general and not compared between groups. Only in the dermatomyositis and polymyositis trial (33), were serum levels of enzymes mentioned for both groups. Moreover, several participants in all trials experienced muscle soreness. An enhanced liability for overwork weakness in more severely affected FSHD patients cannot be excluded, because patients unable to walk independently were not included in the FSHD trial (31). Furthermore, all training studies, including the studies included in this review, imposed a controlled strain for a relatively short period. Hence, exertion of longer duration may still have an undetermined effect on disease progression.

Based on the evidence of the five selected RCTs in this review concerning myotonic dystrophy (14) and myotonic dystrophy type I (30), dermatomyositis and polymyositis (33), FSHD (31) and mitochondrial myopathy (29), people with these specific disorders can be advised that 'normal' participation in sports and work appears not to harm their muscles.
Yet there is still insufficient evidence for general prescription of strength training and aerobic exercise programs in myotonic dystrophy, polymyositis and dermatomyositis and FSHD. Nevertheless, there is some evidence for training effects in mitochondrial myopathy. Unfortunately, no clearly defined exercise protocols can be drawn from the current research evidence.

Evidence from non-randomized studies and other designs, such as pre-post studies or case-control studies showed that aerobic exercise training appears to be safe and effective in adults with various muscle diseases and that strength training appears to be safe and effective in adults with slowly progressive muscle diseases (42, 43) but limitations in the design of these studies prevent valid conclusions. The number of recent studies lacking a randomized controlled design is striking. At least for the relatively frequent muscle diseases, one should aim for randomized controlled training studies. Preferably, homogeneous groups of people with the same muscle disease should be included. When people with different neuromuscular disorders but with similar distribution and severity of muscle weakness participate in the same study, the data should also be presented for each

major type of muscle disease separately to detect possible disease-specific trends. Because we cannot pool the results of the trials in different muscle diseases in this review, it is not possible to define the optimal exercise duration for people with a specific muscle disease.

Specific diagnostic criteria should be given for all muscle diseases included. Information on the severity of the muscle disease in participants should also be presented so as to allow readers to assess the generalisability of the results to other people with the similar type and severity of muscle disease. In trials with a small sample size, participants should be stratified for disease severity. Another related characteristic that may influence outcome is the level of activity (sedentary versus active) at baseline, because in the healthy population untrained persons respond with higher percentages and rates of gain in strength, compared to trained individuals (22). Activity level and change in activity level for each participant should be monitored objectively during the trial period, for example with an accelerometer.

Participants in an active training group may experience additional non-specific benefits (that is, Hawthorne effects), for instance from regular interaction with a skilled therapist, in contrast to those in a non-treatment or usual care group. As it is well known that such Hawthorne effects may affect outcome (44), future studies should preferably have an appropriate control intervention rather than 'no training' in order to assess the specific benefits of aerobic exercise and strength training. For example, the control group might receive weekly counseling sessions with general information about exercise.

In strength training and aerobic exercise intervention studies, the training program should be described in detail, just as the prescription of drugs would be. Authors should provide information about the type(s) of exercises, the intensity (including progression rate), frequency, duration per exercise session, the duration of the entire program, as well as the trained muscle groups, and the supervision of training.
The recommendations from the ACSM Position Stand on 'The recommended quantity and quality of exercise for developing and maintaining cardiorespiratory and muscular fitness, and flexibility in healthy adults' (22) can be used as requirements for an effective, safe and individualized exercise prescription, taking into account the pre-training level of fitness. The ACSM recommendations were almost all adhered to by most of the included and excluded studies in this review. The only criterion that was rarely met was that eight to 10 major muscle groups should be exercised in strength training programs. This is probably partly due to limitations in time available to evaluate the effects of training by multiple

assessments covering the different outcome measures. In addition, expenses for (adjusted) training equipment can be high. Thirdly, investigators were perhaps too cautious in order not to strain participants too much. Moreover, strength training for fewer than eight muscle groups could be adequate in people with a muscle disease, who are generally untrained.

More studies that evaluate the level of basic muscle function and aerobic capacity are needed on the effects of aerobic exercise and strength training programs in people with specific muscle diseases. There are well-validated outcome measures that are able to assess positive and, at least equally important, negative effects on the diseased muscular system. The expertise to deliver training programs in healthy individuals is already present in sports medicine and experts in exercise physiology should be consulted.

If strength training and aerobic exercise training programs prove to be effective for people with a muscle disease, we can then aim to develop and evaluate programs adjusted to each different muscle disease. In people with muscular disorders, combinations of muscle weakness, fatigue, pain and difficulty exercising can all lead to reduced physical activity and a sedentary lifestyle (45). Physical inactivity negatively impacts quality of life and health outcomes (45).

In healthy young adults, in the elderly, and in cardiac patients, increasing physical activity and participation by comprehensive exercise programs incorporating aerobic activities, strength training and flexibility exercises has been shown to reduce the risk of several chronic diseases (for example, coronary heart disease, obesity, diabetes and osteoporosis) (22). Therefore, indicators of chronic disease risk such as blood pressure, resting heart rate, body mass, glucose tolerance and bone density could be useful as additional outcome measures (46), although little is known about the risks of comorbidity in people with a muscle disease. Cost-benefit analyses are only relevant if the benefit of training is much higher than studies have shown so far.

In summary, the authors' recommendations for future studies are as follows.

- Participants with different muscle disorders can participate in one study, but data should be presented for each major type of muscle disease separately.
- Randomized controlled comparisons should be made with participants having the same muscle disease. The effect of training in people with a muscle disease should be compared to a non-exercising control group of people with

the same muscle disease and not to healthy individuals, or to contralateral nonexercised limbs.

🚲 An appropriate placebo intervention is recommended in order to measure exercise-specific benefits.

🚲 Stratified randomization is strongly advised with regard to disease severity, particularly in studies with a small sample size. It should also be considered for pre-training level of activity (sedentary versus active), particularly in aerobic intervention studies.

🚲 The following aspects of the training intervention should be specified: type(s) of exercise training, intensity and progression rate, frequency, duration per exercise session and of the entire program, trained muscle groups, and supervision of training. Duration of the training intervention should be at least six weeks.

🚲 Outcomes should at least include measures of muscle function (for example, strength, endurance measured by the maximum duration of contraction) and aerobic capacity (for example, work capacity measured by an incremental cycle test), and functional assessments such as a six-minute walk test. Researchers should be aware of the specificity of training effects in their choice of outcome measures. The following evaluations are strongly advised: measures of quality of life, pain and experienced fatigue.

🚲 Outcomes assessors should be blinded to interventions, to avoid measurement bias.

🚲 Activity level of participants in the control group should be monitored objectively in order to assess the specific benefits of aerobic exercise and strength training exercise.

AUTHORS' CONCLUSIONS

IMPLICATIONS FOR PRACTICE

Based on the evidence from five RCTs in this review, moderate-intensity strength training in myotonic dystrophy (14) and FSHD (31), aerobic exercise therapy in dermatomyositis and polymyositis (33) and a combination of strength and aerobic exercise training in myotonic dystrophy type I (30) show no harm, but there is insufficient evidence to conclude that they offer benefit. A combination of aerobic exercise and strength training in mitochondrial myopathy shows no harm and could be beneficial for aerobic capacity (29). The small number of included studies and limitations in study design of the other studies prevent general conclusions in other muscle diseases.

IMPLICATIONS FOR RESEARCH

There is a need for more research to establish whether strength training and aerobic exercise training is beneficial in all forms of muscle disease, and to define the optimal exercise programs for people with a muscle disease.

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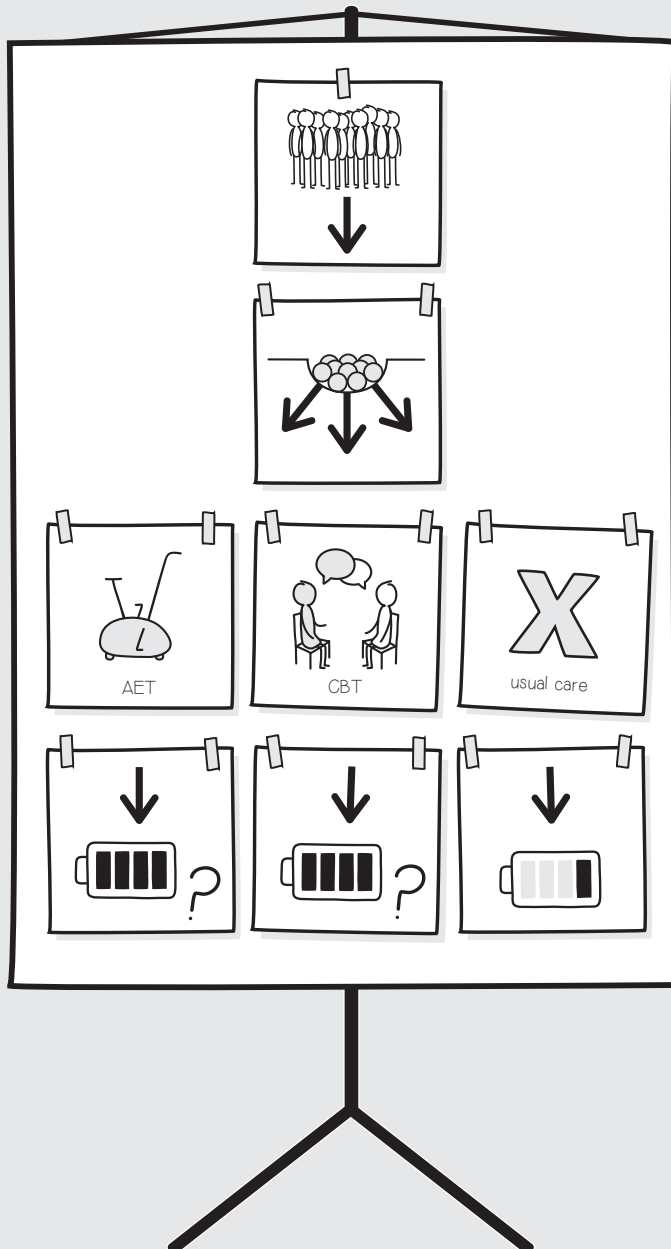
PART 2

FACTS-2-FSHD STUDY
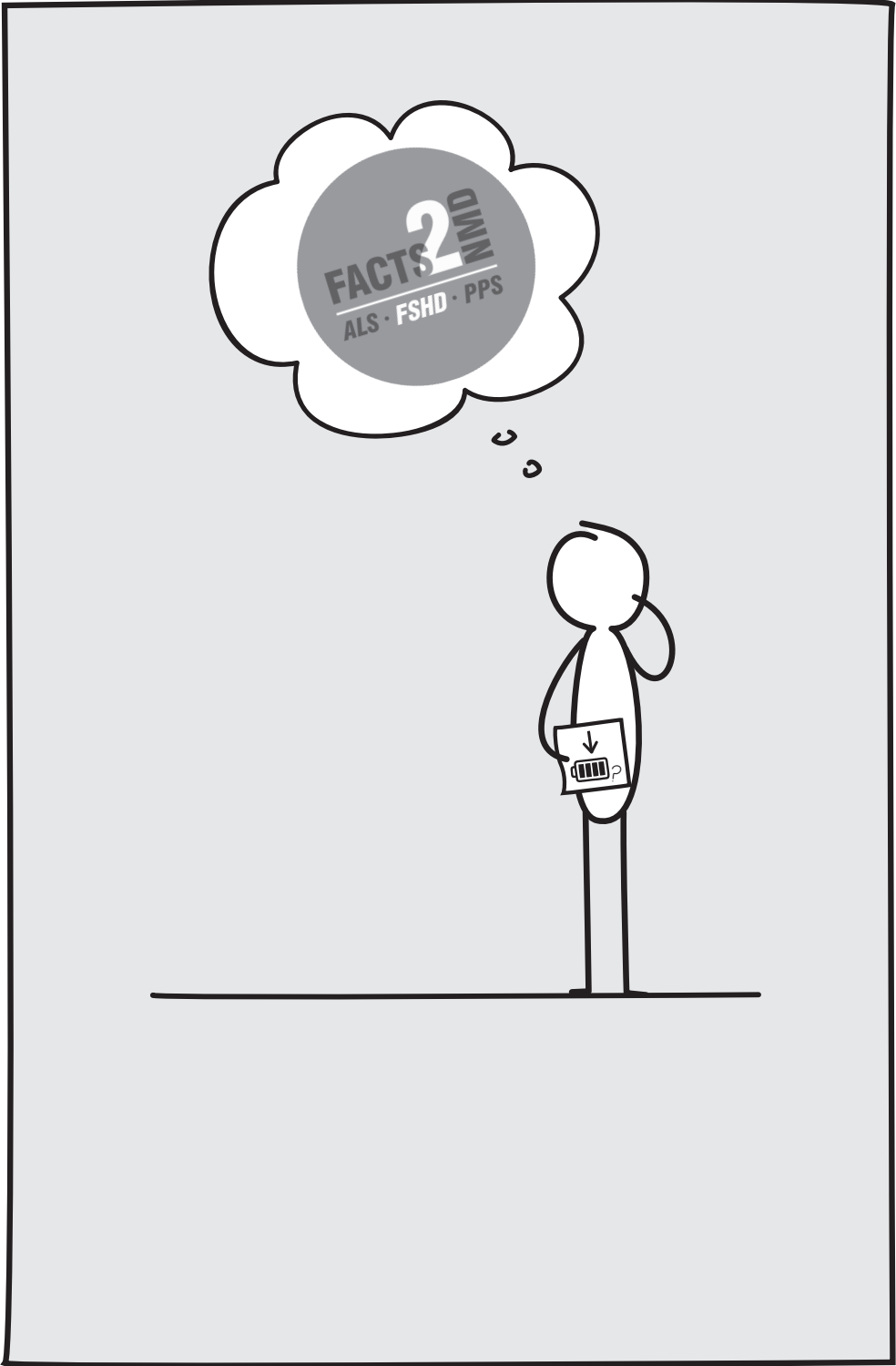
CHAPTER 5

EFFECT OF AEROBIC EXERCISE TRAINING AND COGNITIVE
BEHAVIORAL THERAPY ON REDUCTION OF CHRONIC FATIGUE
IN PATIENTS WITH FACIOSCAPULOHUMERAL DYSTROPHY:
PROTOCOL OF THE FACTS-2-FSHD TRIAL

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ABSTRACT

Background*:*

In facioscapulohumeral dystrophy (FSHD) muscle function is impaired and declines over time. Currently there is no effective treatment available to slow down this decline. We have previously reported that loss of muscle strength contributes to chronic fatigue through a decreased level of physical activity, while fatigue and physical inactivity both determine loss of societal participation. To decrease chronic fatigue, two distinctly different therapeutic approaches can be proposed: aerobic exercise training (AET) to improve physical capacity and cognitive behavioral therapy (CBT) to stimulate an active life-style yet avoiding excessive physical strain. The primary aim of the FACTS-2-FSHD (acronym for Fitness And Cognitive behavioral TherapieS / for Fatigue and ACTivitieS in FSHD) trial is to study the effect of AET and CBT on the reduction of chronic fatigue as assessed with the Checklist Individual Strength subscale fatigue (CIS-fatigue) in patients with FSHD. Additionally, possible working mechanisms and the effects on various secondary outcome measures at all levels of the International Classification of Functioning, Disability and Health (ICF) are evaluated.

Methods/Design:

A multi-centre, assessor-blinded, randomized controlled trial is conducted. A sample of 75 FSHD patients with severe chronic fatigue (CIS-fatigue ≥ 35) will be recruited and randomized to one of three groups: (1) AET + usual care, (2) CBT + usual care or (3) usual care alone, which consists of no therapy at all or occasional (conventional) physical therapy. After an intervention period of 16 weeks and a follow-up of 3 months, the third (control) group will as yet be randomized to either AET or CBT (approximately 7 months after inclusion). Outcomes will be assessed at baseline, immediately post intervention and at 3 and 6 months follow up.

Discussion*:*

The FACTS-2-FSHD study is the first theory-based randomized clinical trial which evaluates the effect and the maintenance of effects of AET and CBT on the reduction of chronic fatigue in patients with FSHD. The interventions are based on a theoretical model of chronic fatigue in patients with FSHD. The study will provide a unique set of data with which the relationships between outcome measures at all levels of the ICF could be assessed.

Trial registration:

Dutch Trial Register, NTR1447.

BACKGROUND

Facioscapulohumeral dystrophy (FSHD) is the third most common inherited neuromuscular disorder. It is an autosomal dominant slowly progressive myopathy with a variable age of onset, mostly in the second or third decade of life. Its yearly incidence rate is approximately 1:20,000 (1). The disease primarily affects the facial muscles, the muscles of the shoulder girdle (most typically the scapula stabilizers) and various leg muscles, while pelvic and trunk muscles are eventually affected as well (2-4). The pattern of muscle weakness is often asymmetrical, and the rate and extent of progression may vary considerably with sudden periods of unexplained rapid disease progression. In a small percentage of the patients, even respiratory insufficiency may occur (5). Only very recently, evidence became available that there may be a selective involvement of the central nervous system as well, in terms of decreased grey matter volume (6) and reduced intracortical inhibition (7). Although FSHD is associated with a partial deletion of a critical number of repetitive elements (D4Z4) on chromosome 4q35, to date no causal gene has been identified and no curative treatment is available (3, 8). FSHD may eventually lead to serious disabilities of speech, swallowing, reaching, standing and walking, even in early adulthood. Twenty percent of the patients become wheelchair bound. Since no cure is available, rehabilitation is the mainstay of treatment (2, 3, 9).

Only recently it was shown by our group that severe fatigue, defined as a score equal as or higher than 35 on the subscale fatigue of the Checklist Individual Strength (CIS-fatigue), was reported by 61% of the patients with FSHD. These severely fatigued patients had more problems with physical and social functioning as well as with mental and general health than similar patients without a severe fatigue. They also had more problems with concentration, initiating and planning (10). As such, experienced fatigue should be clearly distinguished from muscle weakness, which is probably the most common and characteristic symptom of FSHD (11). In a longitudinal study, we built a model of perpetuating factors for fatigue in patients with FSHD (Figure 1). It appeared that lack of physical activity, sleep disturbances and pain all contributed to experienced fatigue. In addition, loss of muscle strength and pain contributed to fatigue through a lower level of physical activity. Ultimately, experienced fatigue and physical inactivity both contributed to the level of societal participation (12). Thus, theoretically, in order to improve societal participation one should improve muscle strength, reduce pain, optimize physical activity and alleviate experienced fatigue. In addition, falling appears to be a major problem among FSHD patients. Our group was able to show that 65% of the patients reported falling at least once a year (13). Since fall incidents often lead

to fear of falling and avoidance behavior, they have a serious negative impact on physical activity and participation.

Improving muscle strength by strength training and/or (anabolic) medication has shown not to be successful in patients with FSHD (14). Until now, only one trial has investigated low-intensity aerobic exercises, indicating that aerobic training is a safe method to increase exercise performance (14, 15). Although, in general, physical activity does not appear harmful (16, 17), more research is needed to establish whether AET is beneficial in patients with FSHD. Besides improving physical (aerobic) capacity, it seems important to optimize physical activity and change behavior in daily life. Indeed, symptoms and signs of muscle weakness and fatigue as well as the anticipation of a (further) decline in physical capacity may elicit an inactive life-style, which may disproportionally affect physical activity, fatigue and societal participation. From this perspective, it might be beneficial to alter illness cognitions and coping styles by means of CBT. However, evidence for the effectiveness of CBT in patients FSHD is not yet available.

The primary objective of the FACTS-2-FSHD trial is:
- to study the efficacy of AET and CBT for decreasing chronic fatigue in patients with FSHD. It is hypothesized that both AET and CBT are more effective in decreasing fatigue than usual care, which is no therapy at all or occasional (conventional) physical therapy. The improvement by AET may be obtained through enhancement of physical (aerobic) capacity, whereas beneficial effects of CBT may be achieved through changes in daily activities and behavior. By changing illness cognitions and improving coping style, the balance between actual behavior and physical capacity will be optimized. Since changes achieved by CBT are more 'intrinsic', possible beneficial effects of CBT may last longer than those of AET.

Secondary objectives of the FACTS-2-FSHD trial are:
- to evaluate the effects of AET and CBT on bodily functions and structures as defined by the International Classification of Functioning, Disability and Health (ICF): lower extremity muscle strength, pain, psychological well being, cardiovascular risk factors, aerobic exercise tolerance, sleeping pattern, as well as biomarkers in blood and urine and structural and metabolic muscle tissue characteristics.
- to evaluate the effects of AET and CBT on the ICF level of activities: physical activity in daily life, self perceived functional status, and fall incidence.
  to evaluate the effects of AET and CBT on the ICF level of participation: limitations in participation and autonomy and quality of life.

🚲 to evaluate the effects of AET and CBT on environmental and personal factors as defined by the ICF: coping style, illness cognitions, concentration problems, motivation, caregiver strain, experienced fatigue of the caregiver, social support and coping of the caregiver.
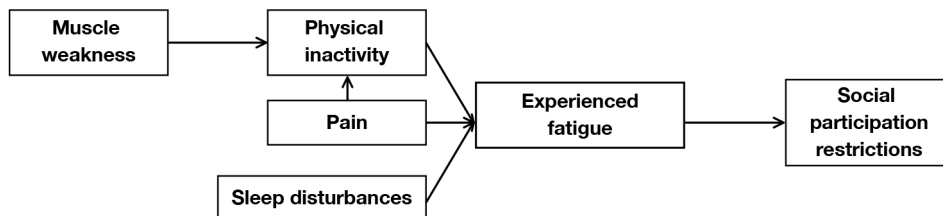

Figure 1 Model of perpetuating factors of experienced fatigue in patients with FSHD

METHODS

STUDY POPULATION

It is intended to include 75 FSHD patients, diagnosed on both clinical and genetic grounds, aged 18 years and older. All patients who participated in previous FSHD studies at the Radboud University Nijmegen Medical Centre (10, 12, 14, 18) are approached by the primary investigator (NV). In addition, all patients known at the departments of Neurology and Rehabilitation of the Radboud University Nijmegen Medical Centre, University Medical Centre of Utrecht, Amsterdam University Medical Centre or any of the affiliated rehabilitation centers are invited to participate as well. In addition, patients who are registered in the Dutch neuromuscular "computer registry of all myopathies and polyneuropathies" (CRAMP) database (19) and/or who are member of the Dutch patient support organization "vereniging spierziekten Nederland" (VSN) will be invited by the primary investigator (NV) and a member of the VSN, respectively, to take part in the study. If the patient is willing to participate, the primary investigator (NV) will check the inclusion and exclusion criteria (Table 1) and estimate the disease severity using the Ricci score (20). When a patient meets all the criteria, oral and written informed consent are obtained according to the declaration of Helsinki. Separate consent is asked to (i) obtain blood and urine samples, and/or (ii) undergo magnetic resonance imaging (MRI) / spectroscopy (MRS), and/or (iii) undergo muscle ultrasound. The study protocol was approved by the Dutch ethical committee CCMO (Centrale commissie mensgebonden onderzoek) and all participating centers granted (ethical) approval to participate.

Table 1 Inclusion and exclusion criteria

Inclusion criteria
(1) age 18 years and older
(2) suffering from severe fatigue (CIS-fatigue ≥ 35) (21)
(3) ability to walk independently (ankle-foot orthoses and canes are accepted)
(4) being able to exercise on a bicycle ergometer
(5) being able to complete either type of intervention

Exclusion criteria
(1) cognitive impairment
(2) insufficient mastery of the Dutch language
(3) neurological or orthopedic co-morbidity interfering with the interventions or possibly influencing outcomes
(4) pregnancy
(5) use of psychotropic drugs (except simple sleeping medication)
(6) severe cardiopulmonary disease (chest pain, arrhythmia, pacemaker, cardiac surgery, severe exertional dyspnea, emphysema)
(7) epileptic seizures
(8) poorly regulated diabetes mellitus or hypertension
(9) clinical depression, as diagnosed with the Beck Depression Inventory for primary care (BDI-PC) (22, 23)

RANDOMIZATION AND BLINDING

Participants fulfilling all inclusion and exclusion criteria are randomized to one of three groups by creating computer-generated 'blocks' ensuring that the same number of participants is allocated to each group. Experimental group 1 (E1) receives AET and usual care for 3 times a week during 16 weeks. Experimental group 2 (E2) receives CBT and usual care once time a week during 16 weeks. Thereafter, both groups are followed up for 6 months. A third group (C) receives usual care only for 16 weeks and serves as a waiting list control group. After another 3-months follow-up (i.e. 7 months after inclusion), this group will as yet be randomized to either AET or CBT for 16 weeks and followed up until 6 months later (total time in study 17 months) (Figure 2). All outcomes are assessed by blinded and independent physical therapists. At the beginning of each assessment, patients are always instructed not to reveal their group allocation to the blinded assessor.
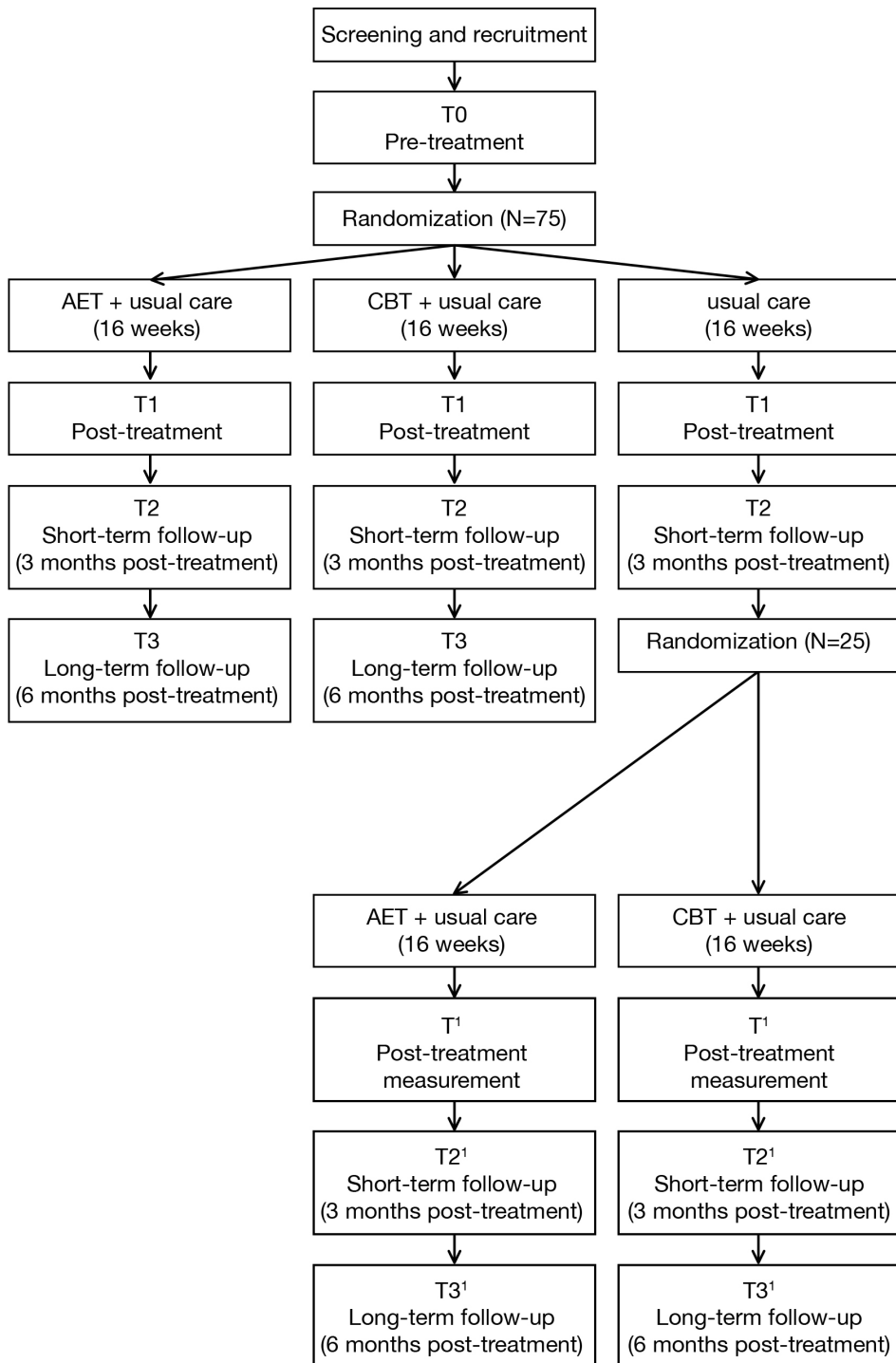
Figure 2 Study design

INTERVENTIONS

Usual care

All participants receive usual care. In the Netherlands, patients with FSHD typically receive no therapy at all, or occasional (conventional) physical therapy. Patients are not restricted in any activities, but all co-interventions are monitored throughout the study by diaries and at every measurement.

Aerobic Exercise Training (AET)

The AET consists of aerobic cycling exercise on a bicycle ergometer. The training program has a duration of 16 weeks and comprises home training twice a week and a supervised training once a week. Training sessions consist of a 30-minute aerobic exercise period with a warming-up and cooling-down period of 5 and 3 minutes, respectively. The cardiovascular load during the training period is individually adjusted and increased from a level of 60% to 75% of the heart rate reserve (HRR). HRR is the difference between the predicted maximum heart rate and the measured resting heart rate. The HRR is equivalent to the difference between the maximum and resting maximal oxygen consumption (VO2max). Each participant is learned how to adjust the physical load to the preferred individual heart rate. Participants are supplied with a Monark 827E bicycle ergometer, a Garmin forerunner 50 heart rate watch with breast belt, and a log book with training instructions at home for the duration of the intervention. During each training, the heart rate is monitored continuously by the breast belt. The number of training sessions, the total time spent on AET, possible adverse effects and the training parameters (physical load, heart rate) are recorded in the individual log book. Once a week, individually supervised training is given by trained physical therapists during one-hour sessions in small groups in a nearby rehabilitation centre. During these sessions, therapy compliance in the home situation is verified by reading out the heart rate watches and checking the log books. In addition, instructions for the next week are provided. The (unblinded) primary investigator and physician (NV) gives instructions to the physical therapists and performs integrity checks at each treatment location.

Cognitive Behavioral Therapy (CBT)

CBT will be focused on the perpetuating factors of fatigue as established in previous research (10, 12, 24) and based on experience in clinical practice. These factors encompass insufficient coping with the disease, dysfunctional illness

cognitions, catastrophizing, dysregulation of sleep, dysregulation of activity, low social support and negative social interactions (see appendix 1 for the various modules). Because of large inter-individual differences, CBT will be adapted to the needs of each patient. For instance, barriers to become more physically active are explored and possibly alleviated in some patients, whereas overactivity is reduced in others. To determine which modules are appropriate, each perpetuating factor is assessed with specific tests, and within each module, the CBT approach is standardized (see appendix 1). The precise number of sessions is dependent on the number of modules.

Each session has a duration of one hour and is given at the most nearby participating centre by a registered cognitive behavioral therapist, especially trained in CBT for FSHD. The therapists have been specifically trained to use the diagnostic tests and indicate the different modules and are regularly supervised by one of the investigators (GB).

COMPLIANCE AND ATTRITION

Therapy compliance is assessed by recording the number of treatment sessions (AET and CBT). For the participants randomized to AET, the total time spent on the bicycle ergometer at home is recorded as well. When applicable, participants are asked for their reasons for poor compliance. In the case of therapy drop out, patients are asked for the reason of non compliance and are stimulated to continue participation in the assessments until the last follow-up.

OUTCOME ASSESSMENT

Outcome measures are listed in Table 2. The primary outcome measure is fatigue severity as assessed with the CIS-fatigue (21). Secondary outcome measures are categorized according to the different ICF levels (25). Outcome measurements are obtained at the Radboud University Nijmegen Medical Centre at the start of the study period (T0), immediately after the intervention period of 16 weeks (T1) and after 3 (T2) and 6 months of follow-up (T3). Observers of the secondary outcome measurements are experienced physical therapists blinded for treatment allocation. At the first measurement (T0), demographic data is obtained by the primary investigator and physician (NV), as well as a general and FSHD related medical history, anthropometric measures (diastolic and systolic blood pressure in mm, resting pulse rate in beats per minute and auscultation of heart and lungs), to verify eligibility. The baseline (T0) and post treatment (T1) visits consist of muscle strength testing of the thigh and aerobic exercise tolerance testing. Participants are asked

to complete the questionnaires and to wear the actometer for 12 consecutive days. An actometer is a motion sensing device that can register and quantify human physical activity and has to be worn at the ankle (26, 27). Blood and urine analyses and MRI, MRS and ultrasound measurements of the thigh muscles are performed. Follow-up measurements (T2 and T3) consist of muscle strength testing of the thigh, aerobic exercise tolerance testing, questionnaires are completed and the actometer is provided.

At the level of bodily functions and structures, patients are asked to give separate consent for several 'invasive' assessments at baseline and after the intervention period. Blood and urine samples are collected by experienced nurses and will be explored by nuclear magnetic resonance (NMR) for possible biomarkers of disease and response to the interventions. Ultrasound measurements of the thigh muscles are made by an experienced ultrasound professional, blinded for the treatment allocation, and analyzed for muscle thickness and echo intensity. In addition, Magnetic Resonance Imaging (MRI) and ^{31}P and proton (^{1}H) Magnetic Resonance Spectroscopy (MRS) are performed by trained professionals, blinded for the assignment to the intervention.

It has been shown that in vivo MRS is able to produce spectra of multiple metabolites simultaneously and is well suited to study energy metabolism in patients with muscular dystrophies (28, 29). The MR examinations start with T1 and T2 weighted images of the thigh for detailed structural analysis. Muscle involvement is specifically assessed by the presence of fatty infiltration on T1 weighted MR images. ^{1}H MRS is used to assess muscle specific creatine as well as extramyocellular lipids and intramyocellular lipids levels, whereas ^{31}P MRS is applied to get information about tissue pH and the level of high energy phosphates.

Table 2 Outcome measures and tests

	Tests
Primary outcome measure	
Fatigue severity	Checklist Individual Strength (CIS subscale fatigue) (30)
Secondary outcome measures	
ICF: bodily functions	
Aerobic exercise tolerance	Maximal oxygen consumption (VO2 max) using the Åstrand protocol (31)
	6-minutes walking test (32)
	Resting heart rate

Table 2 Outcome measures and tests (Continued)

Muscle strength of quadriceps, hamstrings and tibialis anterior muscles	Quantitative Muscle Assessment using fixed myometry testing system (QMA) (18)
Cardiovascular risk factors	Blood pressure* Abdominal circumference Weight / Body Mass Index (BMI) Percentage body fat Visual Analogue Scale (VAS) (33)
Pain	Daily Observed Pain (during a period of 2 weeks) (27, 34)
Psychological well-being and sleeping pattern	Brief Symptom Inventory (BSI) (35)
Metabolic biomarkers	Blood and urine analyses for creatine, glucose, creatine kinase, sodium, potassium, calcium, phosphorus, ureum, ALAT, ASAT, gamma-GT, bilirubine, AF and LDH***
Structural and metabolic muscle characteristics	T1 MRI, T2 MRI, ^{31}P and ^{1}H MRS analysis of muscle specific creatine, extramyocellular lipids, intramyocellular lipids, levels and phosphometabolites in thigh muscles; ultrasound of thigh muscles

ICF: activities

Physical activity in daily life	Actometer, a motion sensing device (during a period of 2 weeks) (26, 27) Daily Observed Spontaneous physical activity (during a period of 2 weeks) (27, 34). Checklist Individual Strength (CIS subscale physical activity) (30)
Self perceived functional status	Sickness Impact Profile (SIP subscales mobility control and mobility range, social behavior) (36)

ICF: participation

Limitations in participation and autonomy Quality of life	The Impact on Participation and Autonomy Questionnaire (IPAQ) (37) 36-Item Short-Form Health Survey (SF-36) (38)
Fall incidence	Telephone computer (weekly calls)**

ICF: personal factors

Coping	Coping Inventory for Stressful Situation (CISS) (30) ALCOS-16 (39)
Illness cognitions	Ziekte cognitie lijst (ZCL) (40)
Concentration problems	Checklist Individual Strength (CIS subscale concentration) (21)
Motivation	Checklist Individual Strength (CIS subscale motivation) (21)

Table 2 Outcome measures and tests (Continued)

ICF: environmental factors

Caregiver strain	Caregiver Strain Index of partner/caregiver (CSI) (41)
Experienced fatigue of patient from perspective of relative.	Checklist Individual Strength (CIS subscale fatigue, filled in by relative about patient) (21)
Experienced fatigue of partner.	Checklist Individual Strength (CIS subscale fatigue, filled in by relative about him/herself) (21)
Social support	Sociale steunlijst-subschaal discrepantie (SSL-D verkort) (42)
Coping of partner	Coping Inventory for Stressful Situations (CISS) (30)

*Measured only at inclusion

** Participants will be called <u>weekly</u> throughout the study by a telephone-computer to obtain fall incidence; in the case of fall incident(s), a subsequent telephone interview is held to obtain information about the cause and circumstances of falling, fall direction, possible injury and ability to get up from the floor

*** In all groups, three extra urine samples will be obtained at week 4, 8 and 12 of the intervention period

An adverse event is defined as any undesirable experience or outcome. Specially assigned site investigators are instructed to report all adverse events immediately to the primary investigator (NV) and to evaluate each event for its date of onset, possible relation to the interventions (based on clinical judgment), possible treatment and course in time. In addition, adverse events can be reported by the participants directly to the primary investigator and physician (NV). All adverse events reported will be carefully monitored and registered until they have abated or a stable situation has been reached.

STATISTICAL ANALYSIS

Generalized estimated equations analysis will be used to investigate differences in the effects on primary and secondary outcome measures between the study groups and to investigate the influence of possible effect modifiers. When necessary, analyses will be adjusted for group differences in fatigue severity and physical activity at baseline. Data will be analyzed according to the intention-to-treat principle.

POWER

In order to detect a 10% group difference (E1 and E2 versus C) in change in fatigue severity between the start and the end of the intervention period (assuming difference in standard deviation between the start and the end of the intervention

(SDdif) = 10%, α = .05, β = .80), 20 participants per group are required. With an expected drop-out rate of maximally 25%, 25 participants will be recruited in each group (n=75).

DISCUSSION

To the best of our knowledge, the FACTS-2-FSHD study is the first randomized clinical trial which evaluates the effect of AET and CBT on the reduction of chronic fatigue in patients with FSHD.

This study has several strengths. First, the selected interventions are based on a theoretical model of chronic fatigue in patients with FSHD (12) and are compared with usual care in a randomized design. Until now, only one randomized controlled trial has been conducted that could not establish a beneficial effect of muscle strength training compared to no training in FSHD (14, 18). In addition, one trial has been conducted that investigated low-intensity aerobic exercises in FSHD. Although this latter study reported improved maximal oxygen uptake and workload as a result of training, this was an uncontrolled and unblinded trial of only 8 patients (15). The majority of the training studies in patients with muscle disorders did not include a (no-training) control group or used healthy subjects as controls. In addition, data are often presented for mixed groups of muscle disorder (17). Second, the proposed study uses a broad arsenal of secondary outcome measures at all levels of the ICF, including 'invasive' measurements of possible biomarkers in blood and urine as well as measurements of structural and metabolic muscle characteristics.

This approach will provide a unique set of data with which it should be possible to accurately assess the relationships between disease characteristics, loss of bodily functions, activity limitations and restrictions in societal participation in patients with FSHD. Third, all patients will be followed up until 6 months after the interventions, which will not only provide information about the maintenance of effects, but also about any long-term adverse events.

A limitation of this study is that the sample size calculation was based on detection of a 10% difference between the intervention groups and the control group, presuming more or less equal effect sizes of AET and CBT. Detecting more subtle differences in the effectiveness between both interventions would require a much larger sample size. In the Netherlands alone, such a trial would not be feasible.

In conclusion, the FACTS-2-FSHD study will increase our insight into the effectiveness of aerobic exercise training and cognitive behavioral therapy to reduce chronic fatigue and to optimize physical activity and capacity in patients with FSHD. A successful outcome of this study has the potential to change existing (inter)national guidelines for physical training and to improve the quality of life in patients with FSHD.

APPENDIX 1 DIFFERENT MODULES OF COGNITIVE BEHAVIORAL THERAPY

Perpetuating factors: insufficient coping with the disease

Insufficient coping with the disease is assessed with the Impact of event Scale (43, 44). A participant can continue to be occupied with the period of being diagnosed with FSHD. By means of talking or writing about this experience (which can be referred to as 'exposure'), the participant will acquire better coping skills. Fear of progression is assessed with a questionnaire especially designed for FSHD. The therapist helps the participant to formulate explicit words to describe the thoughts of fear of progression. These thoughts are challenged against reality (reality testing). In this way, daily unhelpful thoughts about the disease progression are reduced and put into perspective.

Perpetuating factors: dysfunctional cognitions regarding fatigue, activity and other symptoms

Dysfunctional cognitions relate to a variety of ideas, including a participant's idea of lack of control over symptoms, and dysfunctional cognitions about symptoms, such as catastrophizing. The sense of control in relation to fatigue complaints will be assessed with the self-efficacy scale (34, 45).

Perpetuating factors: catastrophizing

Catastrophizing will be assessed with the Jacobsen Fatigue Catastrophizing Scale (46). These cognitions are disputed and more helpful ways of thinking are taught.

Perpetuating factors: dysregulation of sleep

Dysregulation of sleep is based on self-report in a sleep diary (47). An irregular sleep-wake rhythm can perpetuate fatigue. To restore the biologic rhythm, participants are encouraged to adhere to fixed bedtimes and wake-up times and discouraged from sleeping during the day, or they are helped with adapting fixed rest period(s).

Perpetuating factors: dysregulation of activity

Dysregulation of activity is based on activity (stepping) monitoring using an actometer and a physical activity questionnaire (Physical Activity Scale for Individuals with Physical Disabilities (44, 48). Some patients experience fluctuating periods of activity with subsequent periods of rest during a longer period. Others avoid activity because they are concerned that activity increases fatigue; consequently, they are physically inactive. For patients with fluctuating activity levels, a base level should be established by alternating rest and activities to prevent bursts of activity. Once the participant has set a base level, the physical activity program is started, usually twice a day, starting with 5 to 10 minutes of an activity such as walking or cycling. The activity is increased by 1 minute a day each time the activity is performed (ending at a maximum of 2 times 60 minutes minutes per day). The inactive participant will start the activity program immediately. Gradually, physical activities are replaced by other activities.

Perpetuating factors: low social support and negative social interactions

Low social support and negative social interactions are based on the discrepancy subscale of the Social Support List (49). If a participant still has unrealistic expectations of others or perceives a discrepancy between actual support and desired support, the therapist helps to install more realistic expectations toward the participant's social support group. The partner or caregiver will be included in this treatment module.

ACKNOWLEDGEMENTS

AUTHORS' CONCLUSIONS

NV is primary investigator and responsible for data collection and analysis and for drafting the manuscript. AG, BvE, GB, and GP designed and supervised the study. AG and BvE obtained funding for the study. All authors helped in finalizing the manuscript.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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Effect on disease burden

before
AET & CBT

after
AET

after
CBT
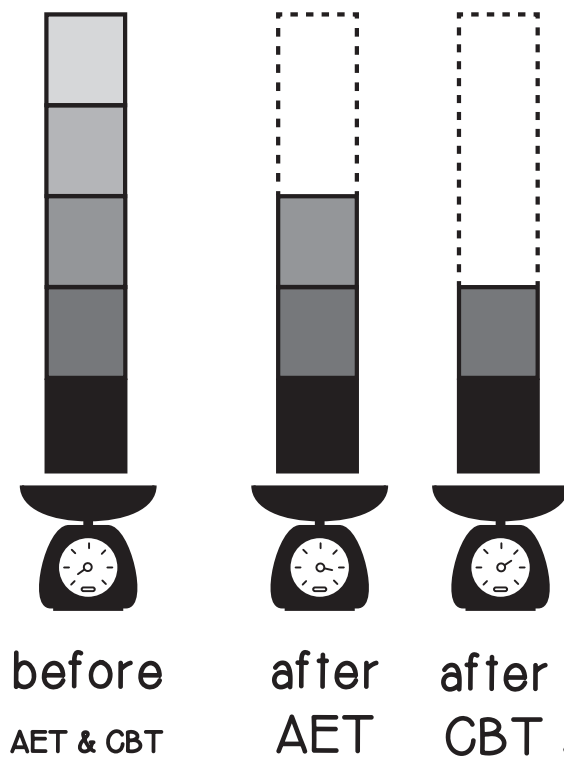
CHAPTER 6

BOTH AEROBIC EXERCISE AND COGNITIVE BEHAVIORAL THERAPY
REDUCE FATIGUE IN FSHD: A RCT

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ABSTRACT

Objective:

To investigate the effect of aerobic exercise training (AET) and cognitive behavioral therapy (CBT) on chronic fatigue in patients with facioscapulohumeral muscular dystrophy (FSHD).

Methods:

We performed a multicenter, assessor-blinded, randomized clinical trial (RCT). Fifty-seven patients with FSHD type 1 with severe chronic fatigue were randomly allocated to AET, CBT, or usual care (UC). Outcomes were assessed before treatment, following 16 weeks of intervention, and after a 12-week follow-up. A linear mixed model for repeated measurements was used to study the estimated group differences.

Results:

Following treatment, both the AET (28 participants) and CBT (25 participants) intervention groups had less fatigue relative to the UC group (24 participants), with a difference of -9.1 for AET (95% confidence interval {CI} -12.4 to -5.8) and -13.3 for CBT (95% CI -16.5 to -10.2). These beneficial effects lasted through follow-up, with a difference of -8.2 for AET (95% CI -12.4 to -5.8) and -10.2 for CBT (95% CI -14.0 to -6.3). The patients who received CBT had an increase in registered and experienced physical activity, sleep quality, and social participation. The patients who received AET had an increase in registered physical activity only. The increase in registered physical activity in both groups and the improvement in social participation following CBT were still present at follow-up.

Conclusions:

This RCT shows that AET and CBT can ameliorate chronic fatigue in patients with FSHD.

Classification of evidence:

This study provides Class III evidence that, in patients with FSHD type 1 and severe chronic fatigue, AET or CBT reduces the severity of chronic fatigue.

Facioscapulohumeral muscular dystrophy (FSHD) is an autosomal dominant, slowly progressive myopathy, affecting approximately 1:8,000 individuals (1). We previously reported that severe fatigue is experienced by 61% of patients with FSHD and contributes considerably to reduced social participation (2). We also developed a FSHD-specific model of fatigue-perpetuating factors (3). Because the patient's level of physical activity plays a central role in this model, it is a logical target for therapeutic intervention. In theory, one can increase physical activity either by improving muscle strength or by optimizing aerobic capacity. Althoug h strength training in patients with FSHD appears to be safe, its beneficial effects are limited (4, 5). In contrast, a pilot study provided evidence that patients with FSHD can benefit from aerobic exercise training (AET) (6). Cognitive behavioral therapy (CBT) is a different type of intervention that can be used to alleviate individually relevant fatigue-perpetuating factors. Several published studies have provided evidence that CBT can reduce fatigue in chronic fatigue syndrome, multiple sclerosis, and cancer survivors (7-9). However, the effect of CBT on fatigue in patients with muscular dystrophy has not been investigated.

METHODS

STUDY OBJECTIVES

The primary objective of this study was to evaluate the effect of 16 weeks of AET or CBT on chronic fatigue in patients with FSHD type 1 compared to usual care (UC) (10) (level of evidence: Class III). The secondary objective was to evaluate the effects of each intervention on the known fatigue-perpetuating factors in these patients (level of evidence: Class III). In addition, we were interested whether CBT, as it focuses on all fatigue-perpetuating factors, might provide longer-lasting benefits than AET.

PARTICIPANTS

All the adult patients with FSHD who participated in any previous study at our center, (2-4) who were registered in a Dutch neuromuscular database, (11) or who participated in a patient support organization were invited to participate. In addition, they were asked to complete the Short Fatigue Questionnaire (SFQ) (12). If a patient was willing to participate, N.V. checked the inclusion and exclusion criteria (Table 1). A diagnosis of FSHD type 1 had to be confirmed by DNA testing (13).

Table 1 Inclusion and exclusion criteria

Inclusion criteria
(1) age 18 years and older
(2) suffering from severe fatigue (CIS-fatigue ≥ 35)
(3) ability to walk independently (ankle-foot orthoses and canes are accepted)
(4) being able to exercise on a bicycle ergometer
(5) being able to complete either type of intervention

Exclusion criteria
(1) cognitive impairment
(2) insufficient mastery of the Dutch language
(3) neurological or orthopedic co-morbidity interfering with the interventions or possibly influencing outcomes
(4) pregnancy
(5) use of psychotropic drugs (except simple sleeping medication)
(6) severe cardiopulmonary disease (chest pain, arrhythmia, pacemaker, cardiac surgery, severe exertional dyspnea, emphysema)
(7) epileptic seizures
(8) poorly regulated diabetes mellitus or hypertension
(9) clinical depression, as diagnosed with the BDI-PC

CIS-fatigue: subscale fatigue of the Checklist Individual Strength, BDI-PC: the Beck Depression Inventory for Primary Care
Source: adapted with permission from Voet et al. (16)

DESIGN

The study was a multicenter, assessor-blinded, randomized clinical trial using repeated measurements. An independent research assistant allocated each participant to 16 weeks of AET, CBT, or UC using a computer-generated randomization block list. The block sizes varied randomly in order to prevent predictability of the allocation process. After 12 weeks of follow-up, after a total of 28 weeks (i.e., period 1), the patients in the UC group were randomly allocated to 16 weeks AET or CBT followed by another 12 weeks of follow-up (i.e., period 2: 28 weeks). The interventions were performed at 9 health care institutions for convenience of the patients

STANDARD PROTOCOL APPROVALS, REGISTRATIONS, AND PATIENT CONSENTS

The study protocol was approved by the regional medical ethics committee (CMO2008/228) and by each institution's local committee. All patients provided oral and written informed consent (14). The design of this study was published previously (15) and was registered as the FACTS-2-FSHD trial in the Dutch Trial Register (NTR1447).

INTERVENTIONS

AET consisted of 3 weekly sessions of aerobic cycling exercises on a Monark (Varberg, Sweden) 827E ergometer; 2 sessions were performed in the patient's home, and the third was supervised by a physical therapist. N.V. performed integrity checks at each study site. The participants cycled for 30 minutes with additional warming-up and cooling-down periods of 5 and 3 minutes, respectively. During the training period, cardiovascular load was continuously monitored with a heart rate belt and watch (Garmin {Olathe, Kansas} Forerunner 50) and adjusted to the individual participant's level. It was aimed to achieve an increase of 50%–65% in heart rate reserve (HRR) (16). Participants who were taking β-blockers were instructed to exercise at a perceived exertion level of 12–14 on the Borg scale (appendix 1) (17). The number and duration of the sessions, the Borg score, the mean and maximum heart rate, and adverse effects were recorded in an individual log book. During the weekly supervised sessions, the physical therapist verified compliance by reading the data recorded by the heart rate watch and by reviewing the log book. In addition, training instructions for the following week were given to the participant. Acceptable compliance with the AET program was defined as completion of a minimum of 40 training sessions.

CBT comprised 6 possible modules based on the known fatigue-perpetuating factors (3) and previous research (8). These modules were directed at insufficient coping with the disease; dysfunctional cognitions regarding fatigue, activity, pain, or other symptoms; fatigue catastrophizing; dysregulation of sleep or activity; poor social support; and negative social interactions (appendix 2). To account for interindividual differences in these factors, the intervention was adapted to the specific needs of each participant, including an individually tailored structured activity program. Each session was 50 minutes in duration and was conducted at the nearest participating center by a cognitive behavioral therapist. The total number of sessions for each participant was based on the number of modules to

be addressed, which were identified by the therapist by performing an interview and specific tests. Acceptable compliance with the CBT program was defined as completion of a minimum of 3 sessions.

The participants in the UC group received no specific treatment for fatigue but occasional physical therapy was allowed. Throughout the study, the participants were not restricted in their activities. Any cointervention (e.g., physiotherapy session) was noted in the log books.

OUTCOMES

The primary outcome measure was fatigue severity, assessed with the fatigue subscale of the Checklist Individual Strength (CIS-fatigue). This scale consists of 8 questions regarding fatigue as experienced during the previous 2 weeks; each question was scored on a 7-point Likert scale (18). A total score ≥35 indicates severe fatigue (3). The CIS-fatigue has good internal consistency (Cronbach a 0.83–0.92), high discriminative validity, and high sensitivity to change in patients with FSHD (3).

The secondary outcome measures were selected to evaluate each factor of the described model (3).
Maximum voluntary isometric strength for the quadriceps was measured using Quantitative Muscle Assessment (19); the highest value of 2 maximal isometric contractions was collected and the average value of the left and right quadriceps strength was calculated.
Aerobic exercise tolerance (VO2 peak, in L/min) was estimated with the Åstrand test (20). Physical endurance was tested with the distance walked during a 6-minute walking test (21).
Participants were asked to wear an ankle actometer for 12 consecutive days (throughout the day and night) (22). Registered physical activity was averaged over the 12-day period and expressed as the average number of body accelerations per 5-minute period. The physical activity subscale of the Checklist Individual Strength (CIS-activity) was used as a measure of experienced physical activity. This subscale consists of 3 questions regarding activity during the previous 2 weeks; each question was scored on a 7-point Likert scale (22).

Pain intensity was assessed with a Visual Analogue Scale (VAS-pain, range 0–100) (23).
Self-reported sleep disturbances were assessed using the 5- item sleep subscale of the Nottingham Health Profile (NHPsleep, range 0–100) (24, 25).

Social participation restrictions were assessed with the social behavior subscale of the Sickness Impact Profile 68 (SIP68-sb, a weighted score ranging from 0 to 572) (26).

For CIS-fatigue, CIS-activity, VAS-pain, NHP-sleep, and SIP68-sb, a higher score indicates poorer outcome.

All adverse events reported by the participants or observed by the therapists were recorded. Participants were called weekly throughout the study by a telephone-computer to obtain fall incidence (27).

PROCEDURE

At baseline, demographic and clinical characteristics were collected, including the Ricci score as a measure of disease severity (28) (Table 2).

Table 2 Baseline characteristics

	UC (n=24)			AET (n=20)			CBT (n=13)		
Characteristics	n	median	range	n	median	range	n	median	range
Age (years)	24	52	(20-79)	20	59	(21-68)	13	49	(24-69)
Gender (male)	24	17	(71%)	20	12	(60%)	13	8	(62%)
Ricci score	24	3.0	(1.5-4.0)	20	3.0	(0.5-4.0)	13	2.0	(1.0-4.0)
Duration of illness (years)	24	16.7	(1.0-49.0)	20	13.0	(1.0-42.0)	13	7.0	(0.0-40.0)
Duration of fatigue (years)	18	5.0	(0.5-25.0)	17	10.0	(1.7-30.0)	12	4.5	(2.0-28.0)
Physical therapy (PT) (n/%)	24	10	(42%)	20	8	(40%)	13	4	(31%)
Sessions PT/patient/week	24	0	(0-2)	20	0	(0-4)	13	0	(0-2)
CIS-fatigue	24	42	(35-51)	20	41	(35-54)	13	43	(35-56)

UC: usual care, AET: aerobic exercise training, CBT: cognitive behavioral therapy, CIS-fatigue: subscale fatigue of the Checklist Individual Strength

The outcome data of the participants in the AET and CBT groups were collected immediately before treatment, immediately following the 16-week intervention period, and 12 weeks postintervention (period 1 and period 2). The outcome data of the UC group were collected at baseline and after 16 and 28 weeks follow-up (period 1). All measurements were performed at the Radboud University Medical Center by 2 blinded physical therapists. At follow-up, N.V. recorded whether the participants had continued their level of activity during the follow-up period.

POWER

The primary outcome is change in CIS-fatigue between the start and the end of the treatment period (16 weeks). Assuming a difference (in change) between the groups of 8 points, a SD of the change of 8 points, $\alpha = 0.05$, $\beta = 0.80$, and applying a Bonferroni adjustment for the number of comparisons, 20 patients are needed per group using a 2-sided t test. We aimed to include 25 patients per group to allow a dropout rate of 25%. We planned to randomize the patients of the UC group (after 28 weeks) to either intervention group, so that a total of 50 patients (instead of 75) would be needed to evaluate 25 patients per group. No further (down) adjustment for repeated measurements was applied to the already low number of patients per group.

STATISTICAL ANALYSIS

A linear mixed model for repeated measurements was used to study group differences in the change per week after treatment of each of the primary and secondary outcomes. The dependent variable was the specific outcome. The independent class variables were treatment (3 levels: AET, CBT, UC) and period (2 levels: first, second). The independent continuous variables were time (weeks since baseline) and the value of the specific outcome at baseline. The intercept of each patient was treated as a random variable. This allows different levels for different individuals. In addition, all first-order and second-order interaction terms between group, time, and period were included in the linear part of the model. At first, we found that, for all outcomes, the factor period and all interaction terms, except the interaction term between time and treatment, never reached the level of statistical significance and that the models were never significantly reduced when these terms were omitted from the model (likelihood ratio test). Second, we also used time as a class variable and found that this never significantly improved the fit of the model to the data (likelihood ratio test). Consequently, in the final model, period and the period-related interaction terms were omitted and time was treated as a continuous variable, as presented above. Finally, the regression per week in

the UC group was estimated using the data of all 3 points of measurement, and the estimated mean group differences with 95% confidence intervals (CIs) were calculated at 16 and 28 weeks. The difference in percentage of patients with severe fatigue (CIS-fatigue score ≥35) was used as an endpoint to calculate the absolute risk reduction (ARR) for both intervention groups compared to the UC group. The number needed to treat (NNT) was calculated as the reciprocal of the ARR. Statistical analyses were performed with SAS version 9.2 for Windows (SAS Institute, Cary, NC). $p < 0.05$ was considered statistically significant.

RESULTS

The flowchart of the patients in the study is shown in the Figure.
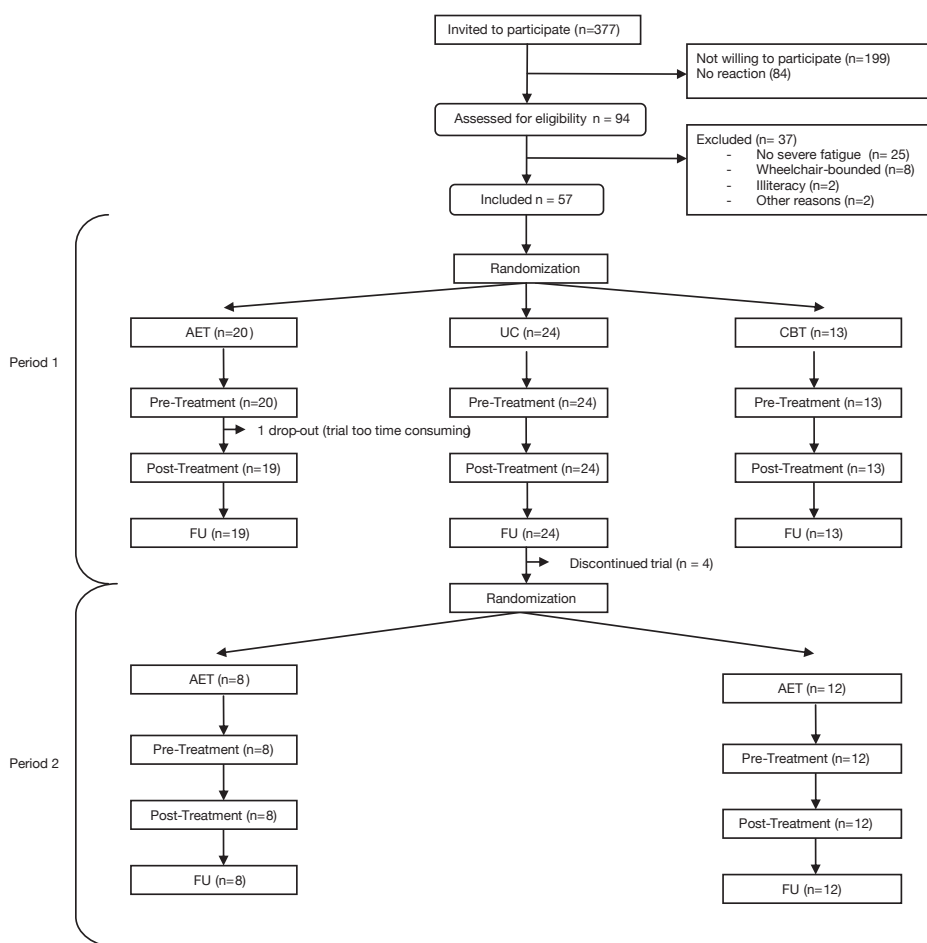
In total, 377 patients were invited to participate. The most commonly cited reason for unwillingness to participate (n = 199) was unknown (n = 153) or the long distance required to travel to the training location (n = 33).

Of the 94 patients who were willing to participate, 57 met the inclusion criteria and were enrolled from January 2009 through February 2012. The nonparticipants were more often female than the participants (50% vs 35%, respectively) and were slightly less fatigued based on their SFQ scores (17.2 vs 19.7, respectively) (12). One participant in the AET group withdrew due to time constraints.
In the UC group, 4 participants withdrew just before the second randomization because they thought that the intervention would be too time-consuming. Thus, after periods 1 and 2, the AET, CBT, and UC groups contained 28, 25, and 24 participants, respectively. During the entire study period, the number of participants receiving co-interventions (physiotherapy only) and the number of physiotherapy sessions remained constant in all groups.

In Table 2, the baseline characteristics are presented. Groups were similar at baseline with respect to demographics, clinical characteristics, amount of physiotherapy, and experienced fatigue. A Kruskal-Wallis one-way analysis of variance indicated that there were no differences between groups either for duration of fatigue (p = 0.37) or for duration of FSHD symptoms (p = 0.30). Post-intervention, the median number of received AET sessions was 42 (range 0–48). Eleven AET participants (39%) did not achieve the level of acceptable adherence. The primary reason for non-adherence was time constraints. Across all AET sessions, the mean exercise time was 30 minutes (SD 1), the mean Borg score was 12.8 (SD 0.3), the mean heart rate was 123 beats/min (SD 12), mean cardiovascular load was 53% HRR (SD 10), and mean work load was 71 Watt (SD 28). Eight participants reached the target training intensity of 65% HRR at the last session. The median number of received CBT sessions was 5 (range 1–13). Six CBT participants (24%) did not achieve the level of acceptable adherence. The most commonly applied modules concerned dysregulation of activity and dysfunctional cognitions.16 At follow-up, 20 AET and 19 CBT participants (71% and 76%, respectively) reported that they had continued their level of activity during the follow-up period.

In Table 3 the observed medians and ranges are presented by group and point of measurement. Note that similar results are observed in period 2 compared to the first period. Especially, the baseline values are similar irrespective of group or period. Post-treatment, the mean experienced fatigue was lower in each intervention group compared to the UC group (AET: mean difference -9.1 {95% CI -12.4 to -5.8}, CBT: mean difference -13.3 {95% CI -16.5 to -10.2}). The beneficial effects were still present at follow-up (AET: mean difference -8.2 {95% CI -12.1 to -4.2}, CBT: mean difference -10.2 {95% CI -14.0 to -6.3}) (Table 4).

Post-treatment, 19 participants (76%) in the CBT group and 14 participants (50%) in the AET group were no longer severely fatigued, as reflected by a CIS-fatigue score, 35. The NNT for AET was 2.3 (95% CI 1.4– 3.1) with an ARR of 50% (95% CI 32–69%). The NNT for CBT was 1.3 (95% CI 1.1–1.7) with an ARR of 76% (95% CI 59–93%). Post-treatment, the mean sleep disturbances, the mean registered physical activity, and the mean experienced physical activity were significantly improved in the CBT group compared to the UC group. In the AET group, only mean registered physical activity was improved compared to the UC group at post-treatment. The beneficial effects regarding mean registered physical activity in the AET and CBT groups were still present at follow-up. The level of social participation restrictions had significantly decreased in the CBT group compared to the UC group post-treatment and at follow-up (Table 4).

Fifteen participants who had received AET reported 1 to 5 adverse events: 4 participants had experienced knee pain, 9 saddle soreness, 7 neck and shoulder pain, and 6 back pain. All these complaints resolved spontaneously during the study period. No adverse events were reported by the participants who had received CBT. For the AET participants, mean fall rate was 0.11 (SD 0.23) times per week during the intervention period, and 0.08 (SD 0.16) times per week during the follow-up. For the CBT participants, mean fall rate was 0.10 (SD 0.21) times per week during the intervention period compared with 0.15 (SD 0.24) times per week during the follow-up. For the UC group, mean fall rate was 0.15 (SD 0.27) times per week. None of the falls occurred during an intervention session. No major injuries occurred as a result of falling.

DISCUSSION

Consistent with our hypothesis, 16 weeks of CBT or AET was more effective than UC for reducing fatigue in patients with FSHD. After a 12-week follow-up without supervision, these beneficial effects remained, probably due to the fact that more than 70% of the AET and CBT participants continued their adjusted level of activity during the follow-up period. Remarkably, these 2 discrete interventions produced quantitatively similar beneficial effects on fatigue, even though the median number of therapy sessions was much lower in the CBT group than in the AET group. This result suggests that CBT is potentially more feasible and cost-effective than AET. As we expected, in the CBT group, all known fatigue-perpetuating factors (with the exception of pain) were positively modified. This finding might explain the higher social participation reported in the CBT group compared to the UC group.

Table 3 The observed median (range) of the outcome measures by group, by point of measurement according to the study design

	Period 1									Period 2								
	Pre-treatment			16 weeks			28 weeks			Pre-treatment			16 weeks			28 weeks		
	n	Median	(Range)	n	Median	(Range)	n	Median	(Range)	n	Median	(Range)	n	Median	(Range)	n	Median	(Range)
Primary outcome measure																		
CIS-fatigue																		
UC	24	42	(35-51)	24	42	(32-56)	24	42	(35-56)	NA	NA		NA	NA		NA	NA	
AET	20	41	(35-54)	19	38	(18-53)	19	39	(11-53)	8	41	(36-47)	8	29	(20-42)	8	29	(24-39)
CBT	13	43	(35-56)	13	24	(12-56)	13	28	(16-56)	12	41	(35-51)	12	30	(8-53)	12	30	(20-42)
Secondary outcome measures																		
MVIC-quadriceps																		
UC	24	19.7	(1.9-40.3)	24	15.0	(2.0-39.5)	23	17.7	(0.9-58.0)	NA	NA		NA	NA		NA	NA	
AET	20	21.0	(10.0-42.7)	19	26.0	(9.1-35.7)	18	24.8	(5.6-47.4)	7	17.7	(3.6-29.9)	8	18.4	(7.5-29.5)	8	18.7	(12.5-31.9)
CBT	13	21.6	(9.2-40.7)	13	20.1	(9.6-33.1)	13	20.7	(9.6-39.1)	12	16.5	(0.9-58)	12	16.1	(4.7-49.3)	12	16.5	(4.8-65.0)
VO2peak" l/min																		
UC	18	2.65	(1.20-5.65)	17	2.50	(1.20-4.30)	16	2.70	(1.50-3.80)	NA	NA		NA	NA		NA	NA	
AET	14	2.50	(1.40-3.30)	11	2.35	(1.70-3.75)	11	2.70	(2.10-3.30)	7	2.35	(1.45-3.20)	7	2.50	(1.20-2.80)	7	2.35	(1.35-2.80)
CBT	10	2.75	(1.60-5.15)	10	2.73	(1.90-4.60)	10	2.80	(1.90-5.15)	8	2.85	(1.60-3.80)	8	2.65	(1.90-4.25)	8	2.90	(1.60-4.45)
6MWT (m)																		
UC	24	436	(80-708)	24	430	(90-800)	23	461	(86-832)	NA	NA		NA	NA		NA	NA	
AET	20	388	(136-630)	18	420	(159-605)	18	450	(157-622)	8	385	(288-648)	8	498	(240-765)	7	455	(300-591)
CBT	13	457	(178-650)	13	440	(210-654)	13	459	(120-733)	11	513	(86-832)	11	480	(120-774)	11	475	(70-799)

The following is a rotated landscape data table (values are medians with ranges). Each measure has three rows (UC, AET, CBT) and six data groups; each cell is given as "n / value / (range)".

Actometer

Group	UC	AET	CBT
1	24 / 38 / (19-74)	17 / 32 / (6-68)	13 / 43 / (21-69)
2	23 / 36 / (10-72)	16 / 38 / (15-65)	13 / 43 / (17-73)
3	23 / 32 / (12-70)	16 / 32 / (1-60)	13 / 41 / (17-65)
4	8 / 30 / (12-42)	11 / 35 / (15-66)	13 / 40 / (15-66)
5	8 / 29 / (17-60)	11 / 35 / (19-74)	12 / 35 / (19-74)
6	NA / NA	8 / 29 / (15-40)	11 / 35 / (18-65)

CIS-activity

Group	UC	AET	CBT
1	24 / 14 / (3-20)	20 / 17 / (4-21)	13 / 14 / (5-21)
2	24 / 13 / (3-18)	19 / 17 / (3-19)	13 / 9 / (13-19)
3	24 / 13 / (3-21)	19 / 13 / (3-21)	13 / 13 / (4-21)
4	8 / 12 / (5-18)	12 / 13 / (5-18)	13 / 20 / (4-21)
5	8 / 14 / (5-20)	8 / 12 / (6-21)	12 / 9 / (3-17)
6	NA / NA	8 / 11 / (6-21)	12 / 10 / (3-21)

VAS-pain

Group	UC	AET	CBT
1	24 / 18.5 / (0-59)	20 / 19.5 / (4-65)	13 / 15 / (0-84)
2	24 / 21 / (0-65)	19 / 20 / (2-65)	13 / 10 / (0-72)
3	24 / 21 / (0-69)	19 / 16 / (0-71)	13 / 10 / (0-80)
4	8 / 13 / (0-47)	12 / 13 / (0-47)	13 / 20 / (0-56)
5	8 / 10 / (0-72)	8 / 10 / (0-72)	12 / 20 / (0-70)
6	NA / NA	8 / 10 / (0-80)	12 / 20 / (0-69)

NHP-sleep

Group	UC	AET	CBT
1	24 / 0 / (0-83.9)	20 / 6.285 / (0-77.63)	13 / 12.57 / (0-61.53)
2	24 / 12.57 / (0-77.63)	19 / 0 / (0-87.43)	13 / 0 / (0-61.53)
3	24 / 12.57 / (0-77.63)	19 / 0 / (0-72.74)	13 / 0 / (0-61.53)
4	8 / 0 / (0-34.27)	12 / 0 / (0-77.63)	13 / 0 / (0-77.63)
5	8 / 0 / (0-21.7)	12 / 12.57 / (0-34.27)	12 / 0 / (0-34.27)
6	NA / NA	8 / 12.57 / (0-21.7)	12 / 0 / (0-21.7)

SIP68-sb

Group	UC	AET	CBT
1	24 / 130 / (0-387)	20 / 187 / (0-572)	13 / 152 / (0-476)
2	24 / 140 / (0-372)	19 / 144 / (0-572)	13 / 149 / (0-387)
3	24 / 169 / (0-572)	19 / 152 / (0-523)	13 / 100 / (0-387)
4	8 / 149 / (0-387)	12 / 149 / (0-572)	13 / 215 / (0-387)
5	8 / 112 / (0-344)	12 / 144 / (0-387)	12 / 144 / (0-420)
6	NA / NA	8 / 137 / (43-386)	12 / 109 / (0-294)

Period: first-, second allocation, Period 1 represents the data of the first allocation and period 2 the data of the allocation of the UC group after the first 28 weeks. NA: not applicable, UC: usual care, AET: aerobic exercise training, CBT: cognitive behavioral therapy, CIS-fatigue: subscale fatigue of the Checklist Individual Strength, MVIC-Quadriceps: average value of maximum voluntary muscle strength in kg for left and right quadriceps, VO_2peak: aerobic exercise tolerance in ml/min, 6MWT: six-minutes walking test in meters, physical activity: the average number of body accelerations per 5-min period, CIS-activity: subscale physical activity of the Checklist Individual Strength, VAS_{pain}: pain intensity on a scale from 0-100, NHP-sleep: subscale sleep of the Nottingham Health Profile, SIP-68-sb: subscale social behavior of the Sickness Impact Profile ***: VO_2 peak data were not available for the six participants who did not reach the target heart rate of 130-170 beats/minute in the 5th-6th minute of the Åstrand test; in addition, VO_2 peak data were not available for 14 participants who took beta-blockers (UC (n= 5); AET (n=6); CBT (n=3)).

Table 4   The estimated mean change since pre-treatment (95% CI) and the estimated mean group differences (95% CI) in all outcome measures by point of measurement, using a linear mixed model for repeated measurements with adjustment for pre-treatment values

| | Change since pre-treatment | | | | | | Difference between groups | | | |
| | UC (n=24) | | AET (n=28) | | CBT (n=25) | | AET vs UC | | CBT vs UC | |
	Mean	(95%CI)	Mean	(95%CI)	Mean	(95%CI)	Mean	(95%CI)	Mean	(95%CI)
Primary outcome measure										
CIS-fatigue										
16 weeks	-1.2	(-3.2 to 0.9)	-8.5	(-12.4 to -4.6)	-13.7	(-17.8 to -9.5)	-9.1	(-12.4 to -5.8)*	-13.3	(-16.5 to -10.2)*
28 weeks	0.0	(-1.7 to 1.8)	-9.1	(-13.4 to -4.7)	-11.1	(-15.6 to -6.6)	-8.2	(-12.1 to -4.2)*	-10.2	(-14.0 to-6.3)*
Secondary outcome measures										
MVIC-quadriceps										
16 weeks	-1.8	(-4.6 to 1.0)	-1.7	(-4.5 to 1.0)	-1.5	(-3.8 to 0.9)	2.1	(0.5 to 4.7)*	-0.2	(-2.9 to 2.5)
28 weeks	0.8	(-1.2 to 2.8)	1.8	(-0.1 to 3.6)	-0.1	(-2.5 to 2.3)	2.3	(-1.3 to 5.9)	0.9	(-3.0 to 4.8)
VO2peak (l/min)**										
16 weeks	-0.4	(-1.9 to 1.1)	0.7	(-1.8 to 3.2)	1.0	(-1.0 to 3.0)	0.1	(-0.1 to 0.3)	0.2	(0.0 to 0.5)
28 weeks	-0.3	(-1.8 to 1.2)	-0.7	(-3.7 to 2.2)	96	(-69 to 260)	0.2	(-0.1 to 0.5)	0.3	(-0.1 to 0.7)
6MWT (m)										
16 weeks	0	(-30 to 30)	31	(-22 to 84)	11	(-20 to 42)	18	(-12 to 48)	-9	(-38 to 20)
28 weeks	9	(-18 to 36)	26	(-15 to 66)	3	(-31 to 37)	15	(-19 to 50)	-12	(-43 to 20)
Actometer										
16 weeks	-1.3	(-5.6 to 2.9)	2.8	(-2.1 to 7.7)	2.9	(0.0 to 5.8)	4.6	(1.4 to 7.8)*	5.6	(1.7 to 9.4)*
28 weeks	-5.3	(-9.3 to -1.4)	-1.6	(-5.2 to 2.0)	0.7	(-1.8 to 3.2)	5.5	(1.6 to 9.3)*	7.1	(1.5 to 12.7)*

CIS-activity										
16 weeks	-1.5	(-3.0 to 0.1)	0.2	(-1.1 to 1.5)	-3.6	(-5.5 to -1.7)	0.6	(-0.8 to 2.0)	-2.6	(-4.1 to -1.2)*
28 weeks	-0.3	(-1.8 to 1.2)	-0.5	(-1.9 to 0.8)	-1.1	(-2.8 to 0.6)	0.6	(-1.3 to 2.5)	-1.1	(-3.0 to 0.8)
VAS-pain										
16 weeks	1	(-8 to 10)	0	(-6 to 5)	4.0	(-3.9 to 11.9)	-2.0	(-10.4 to 6.3)	-0.9	(-8.5 to 6.7)
28 weeks	1	(-6 to 8)	2	(-5 to 10)	4	(-4 to 12)	0.1	(-11.3 to 11.5)	0.0	(-9.5 to 9.6)
NHP-sleep										
16 weeks	3.1	(-4.2 to 10.4)	-0.7	(-6.1 to 4.7)	-6.7	(-17.1 to 3.6)	-0.6	(-6.3 to 5.1)	-7.0	(-12.5 to -1.5)*
28 weeks	-3.1	(-14.2 to 8.1)	0.4	(-5.7 to 6.4)	-8.4	(-17.2 to 0.4)	1.2	(-5.2 to 7.7)	-4.5	(-10.4 to 1.3)
SIP68-sb										
16 weeks	8	(-30 to 47)	-2	(-34 to 29)	-39	(-78 to 1)	-3	(-36 to 31)	-61	(-94 to -29)*
28 weeks	45	(4 to 86)	10	(-26 to 44)	-61	(-116 to -6)	-13	(-50 to 25)	-92	(-127 to 57)

*: Statistically significant differences are marked with an asterisk. All outcomes are secondary other than that set in bold. CI: confidence interval, AET: aerobic exercise training CBT: cognitive behavioral therapy, CIS-fatigue: subscale fatigue of the Checklist Individual Strength, MVIC-Quadriceps: average value of maximum voluntary muscle strength in kg for left and right quadriceps, VO2peak: aerobic exercise tolerance in ml/min, 6MWT: six-minutes walking test in meters, physical activity: the average number of body accelerations per 5-min period, CIS-activity: subscale physical activity of the Checklist Individual Strength, VASpain: pain intensity on a scale from 0-100, NHP-sleep: subscale sleep of the Nottingham Health Profile, SIP-68-sb: subscale social behavior of the Sickness Impact Profile
**: VO2 peak data were not available for the six participants who did not reach the target heart rate of 130-170 beats/minute in the 5th-6th minute of the Åstrand test; in addition, VO2 peak data were not available for 14 participants who took beta-blockers (UC (n= 5); AET (n=6); CBT (n=3)).

In the AET group, the only change in fatigue-perpetuating factors was an increase in registered physical activity. Unexpectedly, we found no improvement in aerobic capacity. This lack of improved aerobic capacity might have been due to insufficient therapy compliance or to the fact that VO2 peak data were not available for the 6 and 14 participants who did not reach the target heart rate or were taking β-blockers, respectively. In addition, the absence of any significant change in isometric quadriceps strength or distance walked in the 6-minute walking test is most likely due to the fact that these capacities were not specifically trained in either treatment group (29).

In this study, only mild adverse effects were found, which, together with an absence of pain increase during the intervention period, suggests that both AET and CBT are safe interventions in patients with FSHD.

A limitation of this study is the potentially low generalizability as only 74 of the 377 invited patients took part. Nevertheless, our study sample was sufficiently heterogeneous with respect to age, disease severity, physical endurance, and level of social participation.

The adherence rate was lower than expected. Especially for AET, practical factors like travel time to the study sites and the fit of the exercise regimen in daily life accounted for the adherence rate being less than 100%. This study provides evidence that AET and CBT can effectively reduce chronic fatigue in patients with FSHD. Future research should focus on the specific factors that contribute to this beneficial effect to optimize patient selection. These studies may also include AET or CBT as part of a more comprehensive treatment program for patients with FSHD and use a longer follow-up period. Tailoring such an intervention program to the specific needs of each patient would meet one of the primary research priorities as identified by patients with a neuromuscular disease (30, 31).

AUTHOR CONTRIBUTIONS

Alexander Geurts, Baziel van Engelen, and Gijs Bleijenberg designed the study and obtained funding. Nicoline Voet included the participants, monitored the study conduct, supervised the physical therapists for data collection, managed and developed the databases, trained the physical therapists, and wrote the first draft. Gijs Bleijenberg trained the cognitive behavioral therapists. Jan Hendriks gave statistical advice and performed the data analysis. All authors contributed to data analysis and interpretation and the writing and editing of the report.

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APPENDIX 1: PROTOCOL AEROBIC EXERCISE TRAINING

The aerobic exercise training (AET) consisted of cycling exercise on an ergometer. The training program had a duration of 16 weeks and comprised home training twice a week and a supervised training by a physical therapist at the most nearby healthcare institution once a week. A cycle ergometer (Monark 827E), a pulse watch with breast belt (Garmin forerunner 50 heart rate), and a log book with training instructions were provided to each participant for home use. Training sessions consisted of a 30-minute aerobic exercise period with warming-up and cooling-down periods of 5 and 3 minutes, respectively. The cardiovascular load during the training period was individually adjusted. Every four weeks, the level was increased with 5% from 50% to 65% of the heart rate reserve (HRR). HRR is the difference between the predicted maximum heart rate and the measured resting heart rate. Resting heart rate was measured during the baseline assessment. Maximum heart rate (MHR) was estimated using the formula: MHR = 220 - age. Each participant was taught how to adjust the physical load to the preferred individual heart rate. During each training, the heart rate was monitored continuously by the breast belt. Participants who were taking beta-blockers were instructed to exercise at a perceived exertion level of 12-14 on the Borg scale. Level of exertion was monitored by heart rate and the Borg visual analog scale. For patients with beta-blocker medication, level of exertion was monitored by the Borg scale alone. The number and duration of the sessions, the Borg score, the mean and maximum heart rate, and any adverse effects were recorded in the individual log book. During the weekly sessions at the healthcare institution, therapy compliance in the home situation was verified by the physical therapist by reading out the heart rate watch and checking the log book regarding the previous week. In addition, individually tailored instructions for the next week were given. The primary investigator (NV) gave instructions to the physical therapists and performed integrity checks at each location. Acceptable compliance with the AET program was defined as a minimum of 40 completed training sessions.

APPENDIX 2: THE VARIOUS MODULES OF COGNITIVE BEHAVIORAL THERAPY BASED ON THE FATIGUE-PERPETUATING FACTORS IN FSHD

Insufficient coping with the disease

Insufficient coping with the disease is assessed using the Impact of Event Scale (33, 34). A participant can continue to be mentally occupied with the diagnosis facioscapulohumeral muscular dystrophy (FSHD). By talking and writing about this experience ('exposure'), the participant can acquire better coping skills. Fear of progression is assessed using a questionnaire designed specifically for FSHD patients. The therapist helps the participant formulate his or her thoughts regarding fear of progression. These thoughts are then challenged against reality ('reality testing'), thereby reducing daily unhelpful thoughts regarding disease progression and putting these thoughts into perspective.

Dysfunctional cognitions regarding fatigue, activity, pain, and other symptoms

Dysfunctional cognitions are related to a variety of unhelpful thoughts, including the participant's feeling of a lack of control over the symptoms and inappropriate thoughts regarding the symptoms. The sense of control in relation to fatigue complaints is assessed using the self-efficacy scale (35, 36).

Catastrophizing

Catastrophizing is assessed using the Jacobsen Fatigue Catastrophizing Scale (37). These thoughts are challenged, and more constructive thoughts are taught.

Dysregulation of sleep

Dysregulation of sleep is assessed using a self-reported sleep diary (38). An irregular circadian rhythm can be a perpetuating factor of fatigue. To restore normal biological rhythm, the participants are encouraged to maintain a fixed bed-time and wake-up time and are discouraged from sleeping during the day.

Dysregulation of activity

Dysregulation of activity is based on activity (e.g. steps) and is monitored using an actometer and a physical activity questionnaire (Physical Activity Scale for Individuals with Physical Disabilities) (34,39). Some patients experience a fluctuating activity pattern, with highly active periods followed by periods of prolonged inactivity. Other patients avoid physical activity because they are concerned that it will increase their fatigue. For participants with fluctuating activity levels, a stable baseline level of alternating resting and active periods is first established. Once the participant has achieved this baseline level, a physical activity program is introduced, beginning with 5-10 minutes of walking or cycling. This activity is gradually increased by 1 minute a day each time the activity is performed, reaching a maximum of two 60-minute sessions per day. Inactive participants are instructed to commence this activity program immediately. Gradually, some physical activities can be replaced with other (preferred) physical activities.

Poor social support and negative social interactions

Poor social support and negative social interactions are determined using the discrepancy subscale of the Social Support List (40). If a participant still has unrealistic expectations of others or perceives a discrepancy between actual support and desired support, the therapist will attempt to instill more realistic expectations with respect to the participant's social support group. The partner or caregiver is included in this treatment module.

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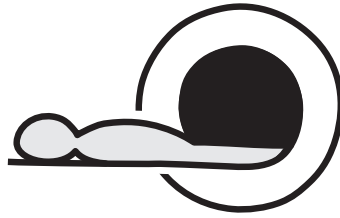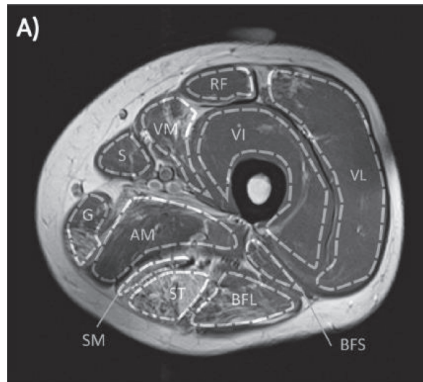
CHAPTER 7

DISTINCT DISEASE PHASES IN MUSCLES OF
FACIOSCAPULOHUMERAL DYSTROPHY PATIENTS IDENTIFIED BY
MR DETECTED FAT INFILTRATION.

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ABSTRACT

Facioscapulohumeral muscular dystrophy (FSHD) is an untreatable disease, characterized by asymmetric progressive weakness of skeletal muscle with fatty infiltration. Although the main genetic defect has been uncovered, the downstream mechanisms causing FSHD are not understood. The objective of this study was to determine natural disease state and progression in muscles of FSHD patients and to establish diagnostic biomarkers by quantitative MRI of fat infiltration and phosphorylated metabolites. MRI was performed at 3T with dedicated coils on legs of 41 patients (28 men/13 women, age 34–76 years), of which eleven were re-examined after four months of usual care. Muscular fat fraction was determined with multi spin-echo and T1 weighted MRI, edema by TIRM and phosphorylated metabolites by 3D ^{31}P MR spectroscopic imaging. Fat fractions were compared to clinical severity, muscle force, age, edema and phosphocreatine (PCr)/ATP. Longitudinal intramuscular fat fraction variation was analyzed by linear regression. Increased intramuscular fat correlated with age ($p<0.05$), FSHD severity score ($p<0.0001$), inversely with muscle strength ($p=0.0001$), and also occurred subclinically. Muscles were nearly dichotomously divided in those with high and with low fat fraction, with only 13% having an intermediate fat fraction. The intramuscular fat fraction along the muscle's length, increased from proximal to distal. This fat gradient was the steepest for intermediate fat infiltrated muscles (0.07 ± 0.01/cm, $p<0.001$). Leg muscles in this intermediate phase showed a decreased PCr/ATP ($p<0.05$) and the fastest increase in fatty infiltration over time (0.18 ± 0.15/year, $p<0.001$), which correlated with initial edema ($p<0.01$), if present. Thus, in the MR assessment of fat infiltration as biomarker for diseased muscles, the intramuscular fat distribution needs to be taken into account. Our results indicate that healthy individual leg muscles become diseased by entering a progressive phase with distal fat infiltration.

INTRODUCTION

Facioscapulohumeral muscular dystrophy (FSHD) is the third most common hereditary muscular disorder (1). The disease is characterized by progressive asymmetric weakness and fatty infiltration of skeletal muscles. In recent years it was demonstrated that FSHD is associated with a contraction of D4Z4 repeats on chromosome 4q35 (2), leading to lost repression of DUX4, a protein that exerts toxic effects on muscle cells (3).

Even though the most important genetic event for the disease seems to be identified, a causative treatment is not yet available (4). Progress is hampered because the trigger for DUX4 expression and the further unfolding of disease processes leading to fatty infiltration and muscle weakness are not known. Thus clarification of the underlying mechanisms is expected to offer clues for a more targeted approach in the search for treatment (5). Understanding these mechanisms first requires that some key questions concerning the process of fatty infiltration are addressed. What is the natural distribution of fatty infiltration? How is this related to clinical severity, to muscle weakness and to energy metabolism? Is there prevalence for specific muscles to be affected and does fatty infiltration vary within muscles? What is the natural progression over time and what are predictive signs of progression? To answer these questions and to evaluate treatment effectiveness, the use of a non-invasive quantitative imaging method, such as MRI, is essential. Unlike biopsies, MRI is not limited to a single location, and longitudinal data can be collected without risk for the patient. MR of fatty infiltration in muscles has been used to study muscular disorders like Duchenne muscular dystrophy (6, 7). We have introduced a quantitative MRI measure of fatty infiltration in muscles based on T2 relaxation time analysis and demonstrated its value in a preliminary study of FSHD patients (8). Phosphorus MR spectroscopy has been used extensively to investigate the energy status of diseased muscles (9-15). Recently it was also introduced in a pilot study with FSHD patients (16).

Until now quantitative MR imaging studies were performed in limited numbers of patients. However, because of the variability in age of onset and in degree of disease severity (17), a study of its pathophysiology requires the participation of a relatively large number of well described patients. The main aim of this study was to determine natural disease state and progression by quantitative MRI of skeletal muscles in the legs of a large, well-characterized cohort of genetically confirmed FSHD patients. In particular we wanted to address the aforementioned pathophysiological questions to ultimately uncover clues on disease mechanism and to establish MRI biomarkers with prognostic and predictive value for personalized assessments.

MATERIALS AND METHODS

PATIENTS AND STUDY DESIGN

We recruited 41 FSHD patients from the local neurology department (28 men/13 women, age 21–81 years, see Table 1 for patients' demographics). Of 36 patients the upper leg ('thigh') was examined, they were selected from a group of patients that were entering a clinical trial to assess the effects of rehabilitation intervention (18). In addition we included the MR exams of the lower leg of five patients from a previous study (8), which were reanalyzed in the exact same way as the MR exams of the aforementioned patients (vide infra).

Eleven patients (8 men/3 women, age 34–76 years) were randomly selected, from the group that underwent an MR examination of the thigh, for a follow-up measurement after a period of four months. During this period these patients were instructed to maintain a normal level of activity ('usual care').

All patients were clinically and genetically diagnosed with FSHD and able to walk independently (ankle-foot orthoses and canes were accepted). Patients were all unrelated except for one mother and son (patients #7 and #37). Disease severity was assessed with the Ricci score (19) and maximum voluntary isometric extension (quadriceps) and flexion (hamstrings) of the knee were measured with a quantitative fixed myometry testing system (20). Ethical approval was obtained from the Radboud university medical center review board, and written informed consent was obtained from all subjects.

Table 1 Patient demographics

Patient nr.	Ricci score	Sex	Age (years)	FSHD duration (years)
1	0	F	21	15
2	1.5	F	25	2
3	1.5	M	31	5
4[*]	2	M	34	3
5[*]	3	M	34	9
6	1.5	M	38	17
7	2	M	38	16
8[*]	3	M	38	19
9	1	F	39	5
10	3.5	M	42	32

11*	2	M	44	14
12	4	M	48	40
13	3.5	M	49	14
14	1.5	F	50	1
15	1.5	F	50	6
16*	4	M	51	19
17*	3.5	M	52	9
18	4.5	F	53	24
19*	3	F	54	1
20*	1.5	M	55	21
21	2	F	55	2
22	2	F	56	22
23	3.5	M	56	17
24	4	M	57	41
25	4	M	57	41
26*	2	F	58	22
27	3	M	59	41
28	4	M	60	9
29	3	M	61	22
30	3.5	M	61	17
31	4	F	63	31
32	4	M	64	15
33	4	M	66	30
34	3	M	66	9
35*	4.5	F	66	49
36	3	M	66	6
37	3	F	68	12
38	2	M	69	Na
39	3	M	69	19
40	3.5	M	76	4
41*	3.5	M	81	3

*Underwent two MR exams four months apart, na = not available,

MR METHODS

MR measurements were performed on a 3T MR system (TIM Trio, Siemens, Erlangen, Germany). Subjects were positioned feet first supine inside the magnet bore. Images were acquired with a home-built proton birdcage radiofrequency coil (inner diameter 25 cm).

In 36 patients, the least affected thigh, according to the subject's own experience was examined, unless there were contraindications (e.g. a previous fracture or recent injury). A fish oil capsule was positioned at one third of the distance between the spina iliaca anterior superior and the patella and served as a landmark for exact matching of the imaging slices between the baseline and follow-up measurements. For the MR examinations of leg, the upper end of the proton coil was positioned at the center of the patella.

MR imaging

Scout images were made in three orthogonal directions to position MRI slices for subsequent scans. The transmit frequency was set on the water resonance and the transmitter voltage was adjusted to the load.

All imaging was performed in the transversal plane centered on the middle femur for the thigh, or the largest circumference for the leg.

T1 weighted spin echo (SE) MR images were acquired first (field of view (FOV) 175 x 175 mm; base resolution 384; repetition time (TR) 530 ms; echo time (TE) 16 ms; slices 23; slice thickness 4 mm; gap 0.4 mm).

Turbo Inversion Recovery Magnitude (TIRM) images were collected with an inversion time (IT) to null the fat signals (FOV 175 x 175 mm; base resolution 256; TR 4000 ms; TE 41 ms; IT 22 ms; slices 23; slice thickness 4 mm; gap 0.4 mm) to visualize edema [21-23]. To avoid inflow artifacts from venous and arterial blood, saturation bands were placed above the upper and below the lower slice [24].

Subsequently, multi SE MR images were acquired (FOV 175 x 175 mm; base resolution 256; TR 3000 ms; 16 equally spaced TE's 7.7–123.2 ms; slices 5–8, limited by specific absorption rate; slice thickness 6 mm; gap 9 mm).

Phosphorus MR spectroscopic imaging (^{31}P MRSI).

A ^{31}P quadrature insert surface coil covered the quadriceps muscles of the thigh, and for the leg measurements a circularly polarized half volume ^{31}P coil covered the calf musculature. A 3D ^{31}P MRSI dataset was acquired after imaging (FOV 150 x 150 x 200 mm; matrix-size 14 x 14 x 8 quadriceps/10 x 10 x 8 calf, TR 1000 ms; BIR45 adiabatic pulse for excitation; 12 averages; weighted k-space acquisition; nominal voxel volume 8.6 ml quadriceps/ 16.6 ml calf). Datasets were interpolated to a matrix size of 16 x 16 x 8.

DATA ANALYSIS

MR imaging

Each of the investigated muscles (see Figure 1) was analyzed separately. T1 weighted images were scored for fatty infiltration using the four grade scale of Lamminen (25), by one experienced musculoskeletal radiologist (J.W.J.R). When a different score was awarded to the proximal and distal images the average score was used.

Muscle area was assessed by drawing regions of interest (ROI's) for every muscle on the center slice of the T2weighted MRI. Fat and muscle fractions were quantified from the multi SE MR images as described earlier (8). Note that normal fat fraction for healthy muscle does not exceed 10% (26). This method is not suitable when edema is present, as it will affect the tissues transverse relaxation properties. In those cases, T1 signal intensity (SI) and TIRM SI of the individual muscles were quantified by carefully drawing ROI's in ImageJ (http://rsb.info.nih.gov/ij/) and normalized to bone marrow SI.

To assess natural progression fat fraction differences were normalized to a period of one year for every patient (for every muscle) by dividing these fractions by the exact number of days between the baseline and follow up measurement, multiplied by 365.25.

^{31}P MRSI.

From the middle slice of the 3D-MRSI dataset with the largest circumference, representative voxels were assigned to a specific muscle according to the corresponding T1weighted image overlaid with the MRSI grid. Only spectra with a sufficient signal-to-noise-ratio (SNR) (Cramer Rao Lower Bound (ɣATP) <30%) were included for further analysis.

Free induction decays were zero-filled to double the number of points and apodized by 8 Hz with a Lorentzian line shape and manually phased using jMRUI 4.0 (27). Peak areas were obtained from inorganic phosphate (Pi), PCr (fitted to a Lorentzian line shape), and ATP (fitted to a Gaussian line shape), using the AMARES algorithm (28) with prior knowledge on the relative line width, frequency and amplitude.
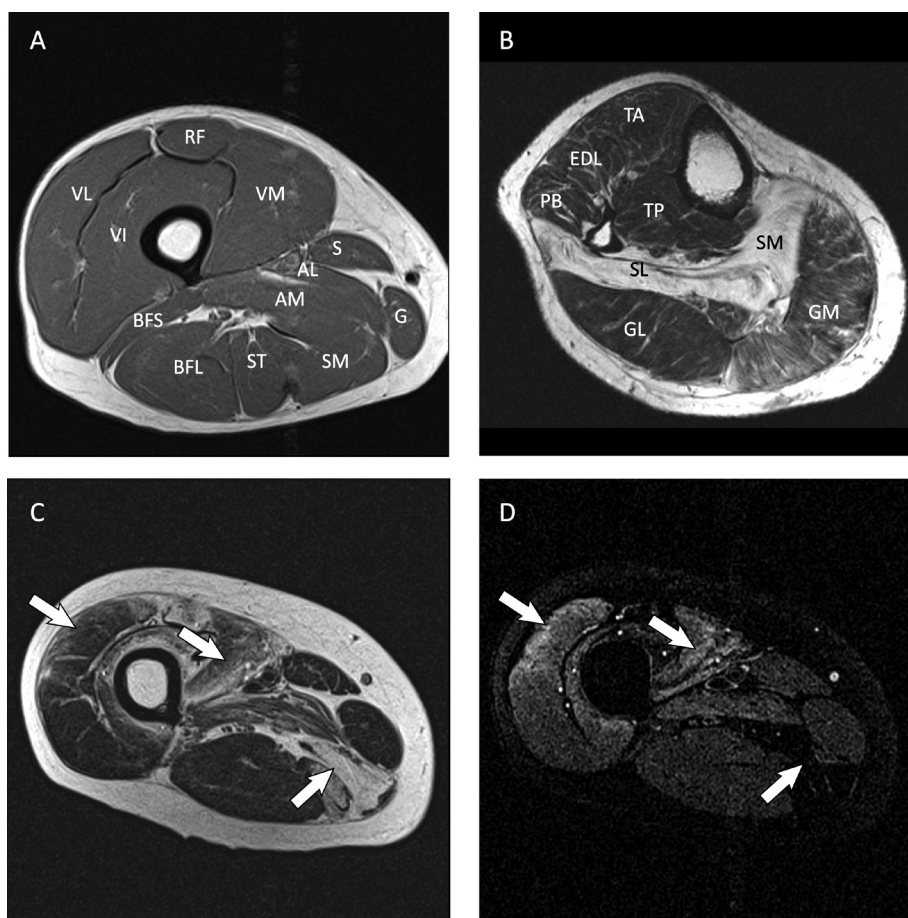
Figure 1 Typical transversal T1 weighted and TIRM MR images of FSHD patients

(A) Transverse T1 weighted image of the thigh of a male FSHD patient (age 38), showing fatty infiltration (hyperintense signal) in the semimembranosus and semitendinosus muscles. (B) Transverse T1 weighted image of the leg of a male FSHD patient (age 66 year). Fatty infiltration of the soleus muscles is clearly visible. (C) Transverse T1 weighted image of the thigh of a 39-year-old male FSHD patient. (D) Corresponding TIRM image. The semi-membranosus is clearly fat infiltrated (grey striped arrow), this results in a nulled signal on the corresponding TIRM image. In contrast, the vastus lateralis and vastus intermedius show hyperintense signal in the TIRM images (white arrows) reflecting edema or inflammation. The different muscles in the thigh (Figure 1A) and calf (Figure 1B) are indicated by the following abbreviations: rectus femoris (RF), vastus lateralis (VL), vastus intermedius (VI), vastus medialis (VM), sartorius (S), adductor longus (AL), adductor magnus (AM), gracillis (G), semi membranosus (SM), semitendinosus (ST), biceps femoris long head (BFL) and biceps femoris short head (BFS), tibialis anterior (TA), extensor digitorum, longus (EDL), peroneus brevis (PB), tibialis posterior (TP), soleus medialis (SOM), soleus lateralis (SL), gastrocnemius medialis (GM) and gastrocnemius lateralis (GL).

Metabolite ratios: PCr/ATP and Pi/ATP were evaluated to avoid coil profile variations. The pH was calculated from the Pi- PCr frequency shift (29). The value of each parameter was averaged for all analyzed voxels in one muscle and this value was used for further analysis.

STATISTICS

Statistical analyses were performed with Prism 5.0 (GraphPad Software, San Diego, California, USA). Non-parametric one-way-ANOVA (Kruskal-Wallis test) was used to investigate differences in the average fat fraction between muscles, with Dunn's Multiple Comparison Test as post-hoc test. One-tailed correlation analyses were performed between fat fraction and patients' age, duration of disease, radiological score, Ricci-scores, maximum voluntary force, PCr/ATP, Pi/ATP, and pH. Linear regression analysis was used to assess the distribution of fatty infiltration over the length of the muscle. Outcome parameters in this analyses are the slope of the line, indicating the direction of fatty infiltration over the length of the muscle, and the coefficient of determination (R^2), indicating to what extent fat fraction increases or decreases linearly over the length of the muscle. One-way ANOVA was used to investigate dependence of fat fraction progression on initial muscle fraction. T1 SI difference was compared between muscles normal and hyperintense TIRM images with a one-tailed t-test, and correlation was investigated with linear regression.

RESULTS

MUSCULAR FAT INFILTRATION, EDEMA, CLINICAL GRADING AND MUSCLE STRENGTH IN FSHD

Fat infiltration in skeletal muscles is visible as hyperintense areas on T1 weighted MR images (Figure 1A–C). This may be accompanied by edema, which can be identified independently from fatty infiltration by TIRM images (Figure 1D). In 41 FSHD patients we investigated 446 leg muscles, of which 4.3% showed edema, which was mostly present in the quadriceps muscles.

The quantitative assessment of muscular fat fraction revealed that 262 of the remaining 427 muscles were normal or mildly fat infiltrated (<0.25 fat fraction), 54 were intermediately fat infiltrated (between 0.25 and 0.75 fat fraction) and 111 muscles were severely infiltrated (>0.75 fat fraction). A fat fraction distribution plot resulted in a typical hourglass shape (Figure 2A). Significant differences were observed in average fat fractions of thigh muscles (p<0.01), in particular the

semimembranosus had a significant higher fat fraction than the vastus lateralis and vastus medialis (Figure 2B).

Average fat fraction correlated positively with patients' age ($p<0.05$, $R^2 =0.15$) (Figure 3A) and FSHD duration ($p<0.0001$, $R^2 = 0.54$), (Figure 3B). Slopes of the correlations were not significantly different between muscles (Figure 4 and 5). The average yearly increase in fatty infiltration was 0.8+/-0.4% for age and 1.9+/-0.3% for FSHD duration.

The average fat fraction showed a strong correlation with radiological scores ($p<0.0001$, $R^2 = 0.70$) (Figure 3C) and with overall clinical Ricci score for FSHD severity ($p<0.0001$, $R^2 = 0.90$) (Figure 3D). The fat fraction deviated from normal at Ricci score 2 (a subclinical event as this score excludes leg muscle involvement) and further increased at higher Ricci scores. Muscle fraction multiplied by the muscle area significantly correlated with muscle strength for the quadriceps and hamstring ($p<0.0001$, $R^2= 0.57$) (Figure 3E).
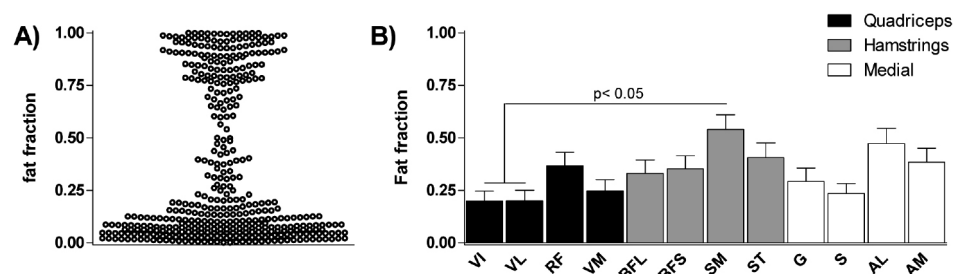

Figure 2 Distribution of naturally occurring fat fraction of the thigh muscles of a large cohort of FSHD patients.

(A) Fat fraction distribution over all muscles. Fat fraction of 0 signifies 100% muscle, 1 indicates 100% fat. Muscles with an intermediary fat fraction (>0.25 and >0.75) are observed, in ~13% of the investigated muscles. (B) Involvement of individual thigh muscles in FSHD. Average fat fraction of 36 patients. Error bars (SEM) reflect the high variability in this fraction between patients. The SM appears to be the most affected muscle of the upper leg, having a significantly higher average fat fraction (0.54±0.41) compared to the VL or VI (0.20±0.29, 0.20±0.27, respectively). Note that fat fractions are not Gaussian distributed therefore reporting only mean±error values is not a good representation of the data.
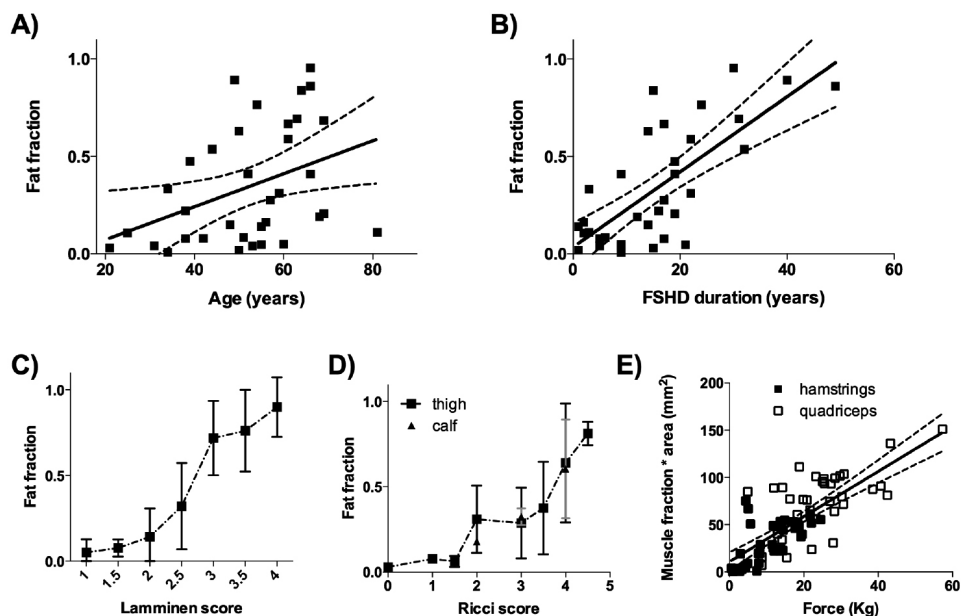
Figure 3 Correlation of fat or muscle fraction, determined by quantitative MRI, with clinical scores

(A) Correlation between age of the patient and average fat fraction of the thigh (p<0.05, R^2 = 0.15). (B) Average fat fraction of the thigh and FSHD duration are highly correlated (p<0.0001, R^2 = 0.54). (C) Fat fraction highly correlates with the radiological Lamminen score of the corresponding muscle (p<0.0001, R^2 = 0.70). (D) Quantitative fat fraction of lower limb correlates with patients Ricci score (p<0.0001, R^2 = 0.90). Fat fraction starts to increase above normal levels at Ricci score 2. The high standard deviation depicted in the error bars signifies the large variation in fat fraction determined in the limb and the appointed Ricci score. (E) Correlation between muscle fraction (1-fat fraction) and force of quadriceps and hamstring muscle groups (p<0.0001 and R^2 = 0.76).

Figure 4 Correlation between fat fractions and age for the individual thigh muscles

Solid line gives best linear correlation with 95% confidence interval indicated by the dotted lines. Slopes of the lines were statistically tested to identify possible differences between the muscles. However analyses showed no significant differences. VL =vastus lateralis, VI = vastus intermedius, RF = rectus femoris, VM= vastus medialis, BFS biceps femoris short head, BFL= biceps femoris long head, S = sartorius, G= gracillis, ST= semitendinosus, SM= semimembranosus, AM= adductor magnus, AL =adductor longus.
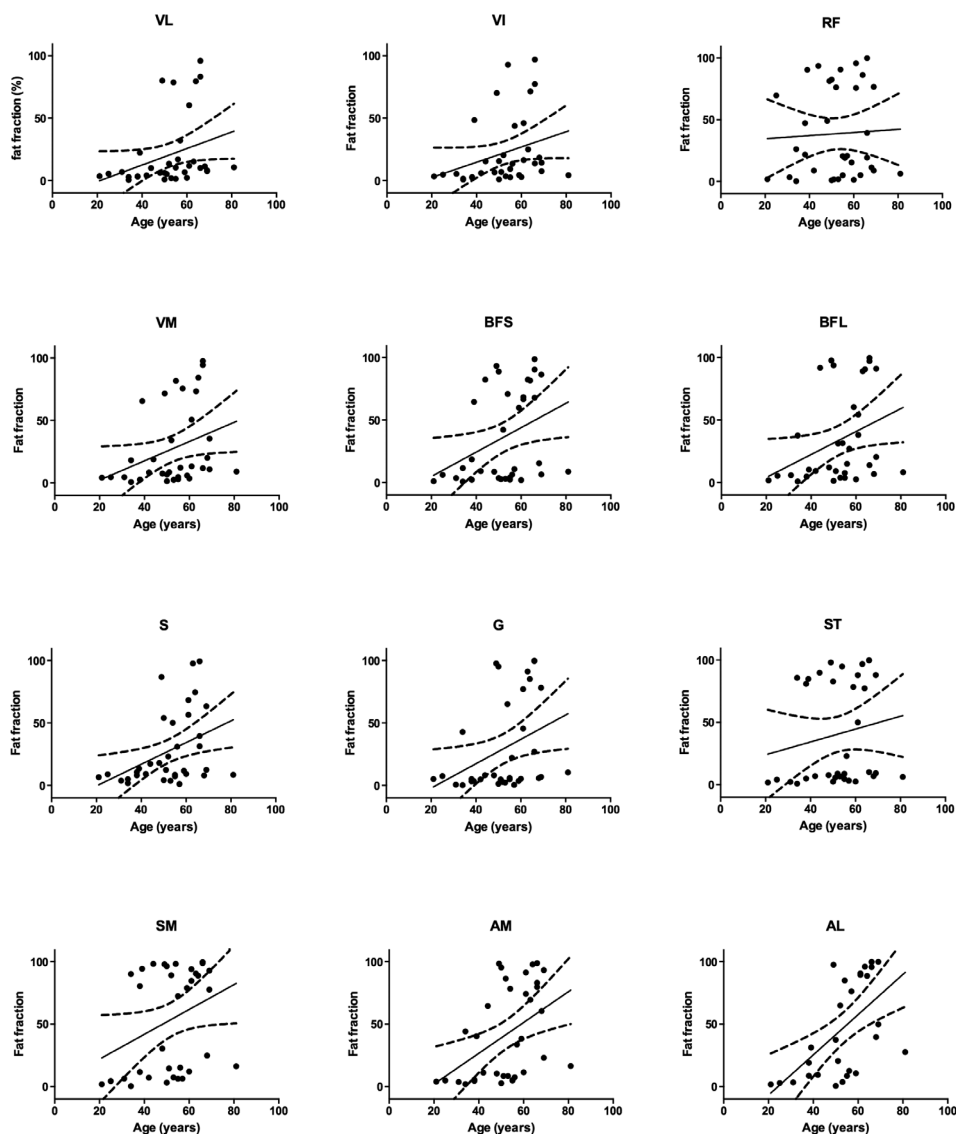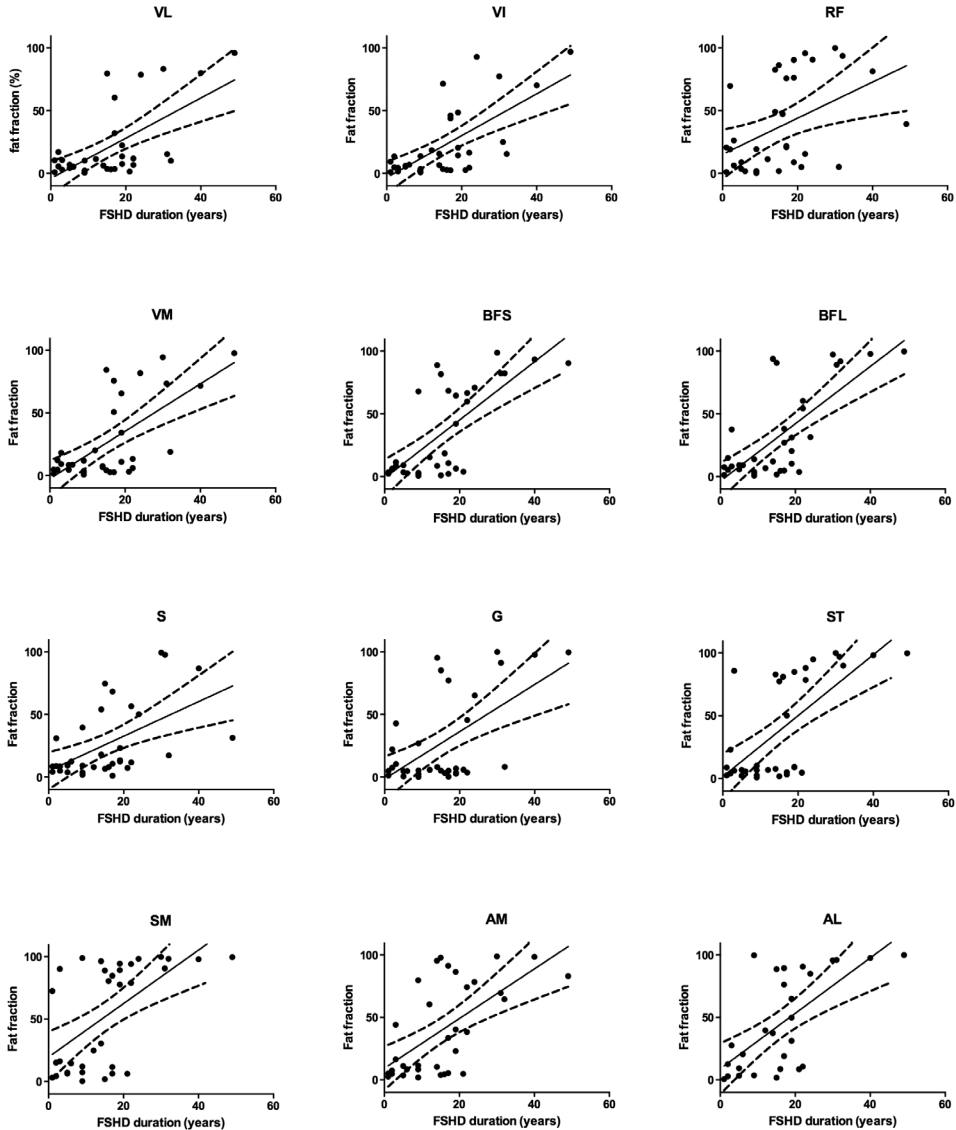
Figure 5 Correlation between fat fractions and disease duration for the individual thigh muscles

Solid line gives best linear correlation with 95% confidence interval indicated by the dotted lines. Slopes of the lines were statistically tested to identify possible differences between the muscles. However analyses showed no significant differences. VL= vastus lateralis, VI= vastus intermedius, RF= rectus femoris, VM= vastus medialis, BFS biceps femoris short head, BFL= biceps femoris long head, S= sartorius, G= gracillis, ST= semi tendinosus, SM= semimembranosus, AM= adductor magnus, AL= adductor longus.

INTRAMUSCULAR FAT DISTRIBUTION

Visual inspection of MR images revealed that the fat fraction was often not evenly distributed over the length of the muscle (Figure 6). Muscle with an intermediate fat fraction showed the steepest fatty infiltration gradient over the length of the muscle ($7\pm1\%$ cm^{-1}, mean$\pm$SEM). This value was significantly higher compared to muscles that were normal or mildly fat infiltrated ($1.3\pm0.3\%$ cm^{-1}, $p<0.0001$) and those that were heavily infiltrated by fat ($1.1\pm0.1\%$ cm^{-1}, $p<0.0001$). Overall fat fraction rose from proximal to distal.
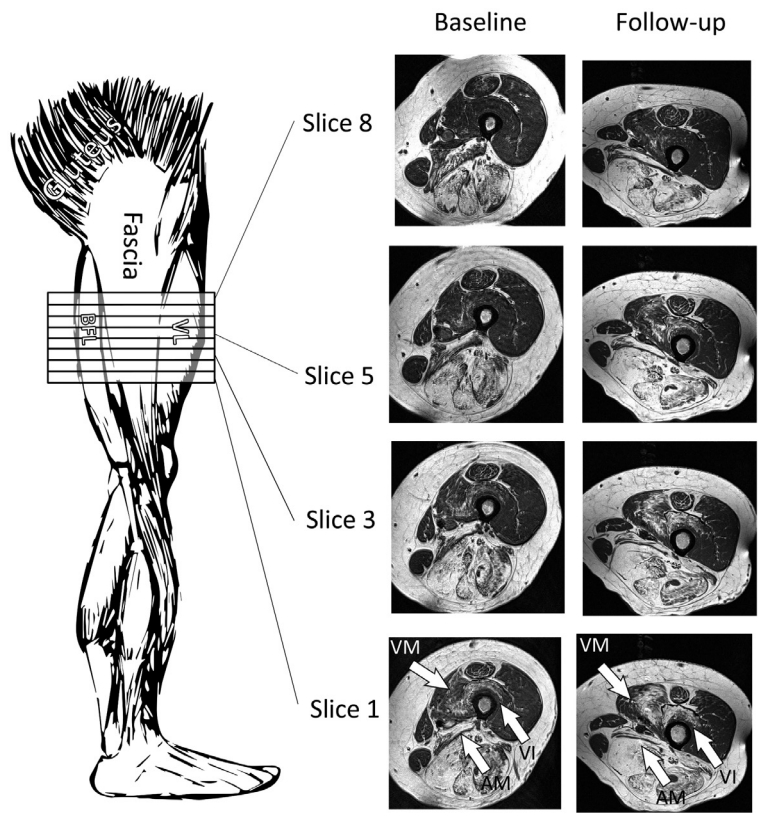
Figure 6 Intramuscular distribution and progression of fatty infiltration

Transversal T1 weighted images at different positions of the thigh of a FSHD patient. Baseline measurement (left panels) reveals an uneven distribution over the length of the muscle with an increasing fat infiltration from proximal (top) to distal (bottom), especially prominent in the VM, VI, AM. This fatty gradient was largest in intermediate fat infiltrated muscles, as was shown by the linear regression analyses. These intermediately fat infiltrated muscles also showed the largest increase in fatty infiltration over time. From the follow-up measurement (right panels) it is clear to see that fat is increasing distally. AM= adductor magnus; BFL = biceps femoris long head; VI = vastus intermedius; VL = vastus lateris; VM= vastus medialis.

NATURAL PROGRESSION OF FATTY INFILTRATION

The natural progression of fatty infiltration was investigated for 85 muscles of eleven patients. An average increase in fat fraction of 0.054±0.12 per year was observed. In intermediately affected muscles (n =12) the progression of fatty infiltration was much faster (0.18±0.15 per year) as compared to heavily fat infiltrated muscles (0.00±0.10 per year, n= 20) and to normal to mildly infiltrated muscles (0.043±0.10 per year, n =53). Natural progression in fat infiltration depended on the initial muscle fraction ($p<0.01$) and appeared to increase from distal to proximal (Figure 6).

Six muscles, in two patients, showed hyperintensity on the baseline TIRM images, indicating edema. The T1 SI difference between baseline and follow up exam, representing fat infiltration, was significantly different in muscles with hyperintense signal on baseline TIRM images compared to TIRM normal muscles (n= 14) of the same patients ($p<0.01$) (Figure 7). Linear regression analysis showed a trend between the TIRM SI and the difference in T1 SI ($p<0.1$, $R^2 = 0.1$).
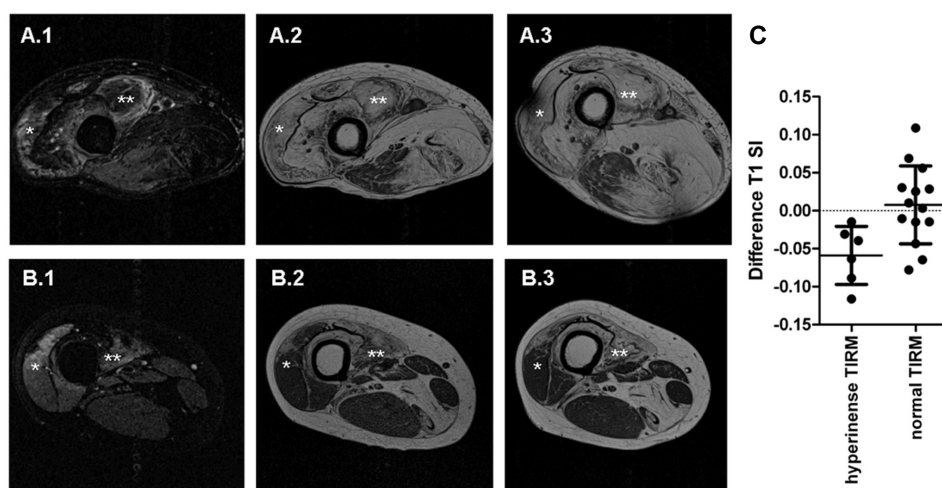
Figure 7 The presence of edema, as identified by TIRM imaging, correlates with increased fatty infiltration, as reflected in changes in T1 weighted images

(A) TIRM and T1 weighted images of a 76 year-old male FSHD patient. (B) TIRM and T1 weighted images of a 39 year-old male FSHD patient. (A–B.1) VL(*) and VM(**) muscles of two FSHD patients show hyperintensity on TIRM images, indicating edema. (A–B.2) Baseline T1 weighted images. (A–B.3) Follow-up T1 weighted images showing an increase of fatty infiltration after about 4 months in the VL(*) and VM(**) muscles. (C) SI difference between baseline and follow-up T1 weighted images is significantly different in TIRM hyperintense FSHD muscles (N = 6) compared to TIRM normal FSHD muscles (n = 14) (p<0.01).

HIGH-ENERGY PHOSPHATE METABOLITES

Analysis of phosphate metabolites by ^{31}P MRS revealed that the PCr/ATP ratio correlated with the fat fraction of the specific muscle (quadriceps $p<0.05$, R^2 = 0.06, calf $p<0.01$, R^2 = 0.33). This PCr/ATP ratio is significantly decreased in the intermediately fat infiltrated muscles compared to muscles with a normal fat fraction ($p<0.05$), but was not further decreased in muscles with a high fat fraction (Figure 8A). The PCr/ATP ratio also correlated with muscle force ($p<0.001$, Figure 8B).
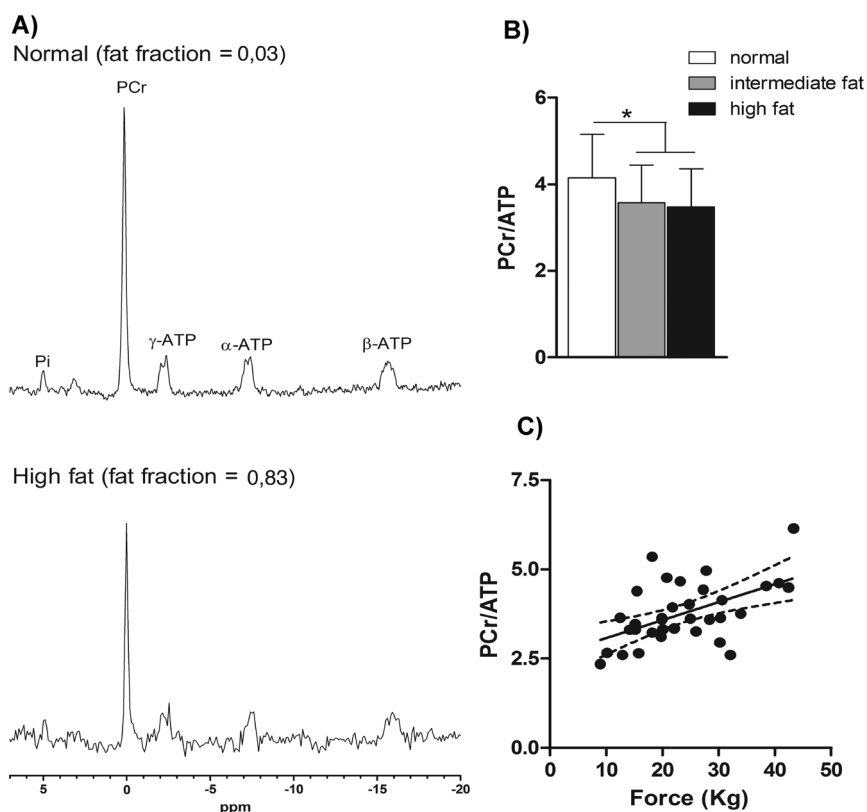
Figure 8 High-energy phosphates in the different stages of fatty infiltration and correlation with muscle force

(A) Representative phosphorous MR spectra of VL muscle of FSHD patients, upper with a normal fat fraction, lower with a high fat fraction. (B) PCr/ATP decreases with fat fraction (mean+/-SD). In intermediately fat infiltrated muscles the PCr/ATP is already decreased significantly from 4.15±1.00 to 3.57±0.88. Completely fat infiltrated muscles do not show a further decrease of this ratio. (C) Significant correlation between PCr/ATP and muscle strength (p<0.001, R^2 = 0.29). Pi = inorganic phosphate; PCr = phosphocreatine; ATP = adenosine triphosphate.

DISCUSSION

In this study we identified three distinct phases of fat infiltration in lower limb muscles of FSHD patients by quantitative MR. An analysis of the average fat fraction for all individual muscles uncovered an hourglass pattern of many muscles with either very here low or high fat, and few muscles with an intermediate fat fraction.

This quasi-binary distribution has not been reported for other muscular dystrophies (7) and may be FSHD specific. The intermediate phase is most characteristic, showing a relative steep fat gradient over the length of the muscles, an altered energy metabolism and rapid progression of fatty infiltration.

For other dystrophies often average values of all subjects or muscles are presented, which obscures the presence of a specific distribution. The average fat fraction as calculated over all investigated muscles in this study (0.3±0.1), actually only was present in 36 out of 427 muscles. Fat fractions were highest in the semi membranosus, semitendinosus and adductor muscles as has been previously described by Wattjes et al. (21). The vastus muscles were largely preserved.

We found that in leg muscles the intramuscular fat fraction increased linearly from proximal to distal, as was also observed in a pilot study of only the lower leg (8). The steepest fat gradient occurred in the intermediate affected muscles indicating that these muscles are progressing towards a complete fat infiltrated state. This interpretation is supported by the follow-up measurements, which revealed that intermediate affected muscles were most prone to increase their fat-muscle ratio. In these muscles the average increase of this ratio was about 10% in four months. This may seem fast for a disease that is characterized by slow progression, but we observed it in only a relative small fraction of muscles. The quasi-binary fat distribution of muscles in FSHD patients mentioned above also indicates that relative rapid transitions occur. Moreover, a sudden disease progression within individual muscles is in accordance with the often reported observation in FSHD patients of periods of rapid deterioration of single muscles or muscle groups, interrupting long stable periods (30, 31). In some cases the lower performance of a single muscle may be compensated by unaffected synergistic muscles, which would clinically mask its dysfunction (32, 33).

Assuming that replacement of muscular tissue by fat occurs at a constant rate after entering this intermediate phase, fat replacement of entire muscles will, on the average, be completed within approximately three and a half years. This can be relevant for prognostication and monitoring therapy effectiveness in FSHD. There is no report on fat gradients over the length of muscles in other neuromuscular

disorders, which may be FSHD specific. Recently, a muscular fatty content gradient was also found in inherited poly-neuropathy, but this was not associated with disease progression (34).

The low percentage of muscles involved in a rapid progression towards complete fatty infiltration indicates that this process is triggered by an infrequent event. The nature of this event is unknown, but the initial relatively high distal level of fatty infiltration and the differences between muscles suggests a local origin. This is in agreement with findings that only 0.1% of muscle nuclei express DUX4 in FSHD patients (35). A recent paper by Tassin and colleagues (36) describes a model of initiation and propagation of a transcriptional cascade, which provides an elegant explanation for our observation of a gradient of fatty infiltration and fast progression in intermediate fat infiltrated muscles. In this model the activation of the DUX4 gene in (one or) few myonuclei yields DUX4 protein molecules that diffuse into the cytoplasm towards neighboring nuclei where they activate target genes, which causes expansion into a transcriptional cascade of dysregulation. Because of the multinucleated nature of myofibers this model predicts a gradient of dysregulation over the length of muscles. The amplification of DUX4 gene activation into a transcriptional cascade may also explain the fast progression observed in the intermediate fat infiltrated muscles. Preferential involvement of particular muscles (e.g. semimembranosus) and distal initiation may hide clues towards the initial DUX4 gene activation trigger. Our finding that MR visible fat content increases more in the case of initial edema supports the involvement of inflammation in early disease onset, as TIRM positive muscles are associated with muscle inflammation (21-23, 37-39). However, whether inflammation is cause or consequence of DUX4 transcription in the initiation process remains unclear.

The correlation between increased fat fraction and lower strength of skeletal muscles is coherent with the loss of muscle mass and also explains the (weak) relation with the age of the patients. Clinical severity scores (Lamminen (25) and Ricci (19) strongly correlated with fat fraction, but abnormal high fat fractions were also present in lower limb muscles without clinical symptoms, as was observed in patients with Ricci score 2 (excludes lower limb involvement). Thus, imaging fatty infiltration is a potential tool to predict clinical muscle affliction (32, 33). The extent of edema in our study (4.3%) is somewhat lower than reported in two recent FSHD studies, that however, included more muscles per patient and more severely affected patients (23, 39, 40).

The lower PCr/ATP ratios observed in intermediately fatty infiltrated muscles suggest an early change in high-energy phosphate metabolism in disease

development. Lower steady state PCr/ATP ratios were also found in muscles of Becker and Duchenne patients (10, 41). This may represent a lower cellular (phospho)creatine pool due to a lower energy state. Alternatively, it may represent a change in fiber type composition, if the fraction of oxidative fibers, which have lower PCr/ATP ratio's (42, 43), increase due to preferred involvement of type II fibers. This is supported by histological findings of biopsies, showing more dominant type I fibers among the remaining fibers in FSHD affected muscles (44) and is also congruent with the correlation between PCr/ATP and muscle force.

Taking muscle biopsies remains the gold standard to examine muscular dystrophies, but this is invasive, painful, restricted to a limited number of biopsy sites and only provides focal information.
As observed in the present and a previous study (8) fatty infiltration is very heterogeneous, both between and within muscles, which demonstrates the need to know in advance which (part of a) muscle is affected, to acquire representative tissue. Our study indicates that MRI guidance in taking muscle biopsies is needed. Other common imaging techniques have disadvantages, such as radiation exposure in computer tomography, or poor signal to noise and limited penetration depth in ultrasound. In clinical trials muscle strength is often assessed to evaluate treatment effects, but this may show a placebo effect (45). Muscular fat fraction determined by MRI does not involve a placebo effect.

A limitation of our study was the lack of including a component for the presence of edema in the T2 analysis. However, we identified muscles with edema by TIRM and excluded the very small fraction of edematous muscles from this T2 analysis. Progression of fatty infiltration in these muscles was then derived from T1 images. Furthermore, we chose to investigate lower extremity muscles in these patients even though FSHD is a disease known to first involve the facial and scapular muscles. However, for this study we aimed for the highest image quality, which could be achieved with a dedicated coil for the lower extremity. To compare different disease phases we had to introduce fat fraction cut-off values, for which we chose 25% and 75% of fatty infiltration. Shifting these values by 65% did not change the main results of this study.

In conclusion, this study established fat fraction as assessed by MR imaging as an objective quantitative and sensitive biomarker for muscular affliction in FSHD, detecting even subclinical muscle involvement. This MR biomarker may serve to predict disease progression, to guide biopsies and to evaluate treatments to preserve or improve muscle performance. Importantly, in these applications the intramuscular fat distribution may have to be taken into account. Our data suggest

a specific sequence of events that leads towards full muscle pathology in FSHD, in which muscles first progress from normal to being distally fat infiltrated, with an altered metabolic profile, after which fat rapidly infiltrates the whole muscles. This process of disease unfolding may direct new treatment strategies.

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AUTHOR CONTRIBUTIONS

Conceived and designed the experiments: AG BE GP AH. Performed the experiments: BJ NV CN HK. Analyzed the data: BJ NV CN HK JR. Wrote the paper: BJ NV CN HK JR AG GP BE AH.

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Fat fraction in vastus muscle
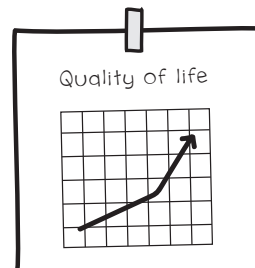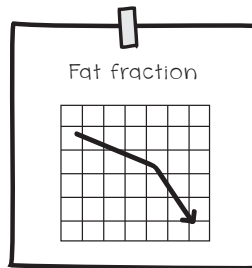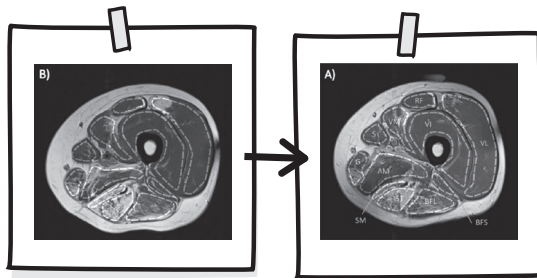
after 16-28 wks CBT & AET

CHAPTER 8

QUANTITATIVE MRI REVEALS DECELERATED FATTY INFILTRATION
IN MUSCLES OF ACTIVE FSHD PATIENTS

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ABSTRACT

Objective:

To investigate the effects of aerobic exercise training (AET) and cognitive behavioral therapy (CBT), directed towards an increase in daily physical activity, on the progression of fatty infiltration and edema in skeletal muscles of facioscapulohumeral muscular dystrophy (FSHD) type-1 patients by T2-MRI.

Methods:

Quantitative T2-MRI (qT2-MRI) and fat-suppressed T2-MRI of the thigh were performed at 3 Tesla on 31 patients, of whom 13 received usual care (UC), 9 AET, and 9 CBT. Muscle-specific fat-fractions (%), derived from qT2-MR images, were recorded pre- and post-treatment. Intervention effects were analyzed by comparing fat-fraction progression rates of the UC with the treated groups using Mann-Whitney tests, and intermuscle differences by a linear mixed model. Edematous hyper-intense lesions were identified on the fat-suppressed T2-MRI.

Results:

The intraclass correlation-coefficient for reproducibility of qT2-MRI fat-assessment was 0.99. In the UC group the fat-fraction increased with 6.7/year (95% CI: 4.3 to 9.1). This rate decreased to 2.9/year (95%CI: 0.7 to 5.2) in the AET (p=0.03) and 1.7/year (95%CI:-0.2 to 3.6) in the CBT group (p=0.00015). The treatment effect differed among individual muscles. Less new edematous lesions occurred after therapy.

Conclusion:

Fat-fraction derived from qT2-MRI is a reproducible and sensitive biomarker to monitor the effects of increased physical activity in individual muscles. This biomarker reports a favorable effect of AET and CBT on the rate of muscular deterioration in FSHD as reflected in decelerated fat replacement.

Classification of evidence:

This study provides Class II evidence that for patients with FSHD type 1, both AET and CBT decrease the rate of fatty infiltration in muscles.

INTRODUCTION

Facioscapulohumeral muscular dystrophy type-1 (FSHD) is one of the most frequently occurring myopathies (1). It is characterized by asymmetric progressive loss of muscle strength and increased fatigue and proceeds with transient edema and fatty infiltration in skeletal muscles (2-4). Although the main genetic origins for FSHD are understood and molecular targets for treatment have been proposed, no cure is available yet (5, 6).

Recent randomized clinical trials (RCTs) demonstrated a positive effect of aerobic exercise training (AET) and cognitive behavioral therapy (CBT) on fatigue and physical activity (7) and of AET on physical fitness and walking distance (8) in FSHD patients. However, outcome measures for muscle strength did not show treatment effects (7-10). Thus, more sensitive quantitative biomarkers at the level of individual muscles are needed to monitor therapies.

Fat infiltration and edema in muscles can be detected by T2-MRI (11-13). We presented fat-fraction determined with quantitative T2-MRI (qT2-MRI) as a non-invasive biomarker for affected muscles in FSHD patients and showed that it highly correlates with clinical severity and muscle strength (14). Moreover, this biomarker has prognostic value and allows to detect subclinical involvement and to follow disease progression in individual muscles (15). Hyperintense areas on fat-suppressed T2-weighted MRI's of muscles, reflecting edema indicative of inflammation (16), have been shown to precede fatty replacement in FSHD muscles (15, 17). Thus, T2-MRI biomarkers seem to be suited to objectively monitor the effects of physical activation therapy in FSHD. Therefore, we examined if qT2-MRI with fat-fraction as biomarker can detect an effect of AET and CBT on the progression of fatty infiltration in individual thigh muscles of FSHD patients.

METHODS

STUDY OBJECTIVES

The primary objective of this study was to evaluate the effect of 16 weeks of AET or CBT on the rate of fatty infiltration in thigh muscles of patients with FSHD type 1 (level of evidence: Class II).

STANDARD PROTOCOL APPROVALS, REGISTRATIONS, AND PATIENT CONSENTS

We invited all patients included in the FACTS-2-FSHD randomized controlled trial to take part in the present MR study. This trial aimed to assess the effects of AET and CBT on fatigue in FSHD [18]. For all patients, the FSHD type-1 diagnosis was confirmed by DNA tests with verification of the 4q35 deletion [19]. Exclusion criteria, in addition to those for the RCT, were MR contraindications such as claustrophobia or the presence of a pacemaker [18].

STUDY SETUP

The RCT was listed in the Dutch Trial Register (NTR1447) and its design was published [18]. Each participant was randomly allocated to usual care (UC), AET, or CBT using computer-generated randomization by an independent health professional who was blinded for the allocation sequence.

Baseline demographics (age and gender) and FSHD severity (10-grade clinical severity scale (CSS)) [20] were collected. All clinical and MRI measurements were performed at the Radboud University Medical Center by two experienced physical therapists and two experienced MRI technicians, respectively, who remained blinded for treatment allocation throughout the study. MRI exams were performed at baseline and at follow-up, which is 12 weeks after the baseline MR in the UC group and 16 weeks therapy plus 12 weeks of UC after the baseline MR in the AET and CBT groups. This ensures that all three groups had equal usual care periods before the follow-up MR exam.

INTERVENTIONS

The therapy interventions were delivered at nine healthcare centers across the Netherlands [18]. Participants in the AET group were asked to cycle three times a week for 30 minutes on an ergometer. During successive training sessions exercise intensity was gradually increased from 50 to 65% of heart-rate reserve. Cardiovascular load and compliance were continuously monitored. The CBT intervention was given by a cognitive behavioral therapist and consisted of six modules which were directed at the known perpetuating factors of fatigue in FSHD: insufficient coping with the disease; dysfunctional cognitions regarding fatigue, activity, pain, or other symptoms; fatigue catastrophizing; dysregulation of sleep; poor social support and/or negative social interactions. For every patient,

a physical activity program was included, starting with 5 to10 minutes of walking or cycling, gradually increasing with 1 minute every day, reaching a maximum of two 60-minute sessions per day. The participants in the UC group received care as usual which in most patients was no treatment or occasional (conventional) physical therapy.

PHYSICAL CAPACITY MEASURES

Participants were asked to wear an actometer around the ankle for 12 consecutive days (21). Physical activity was averaged over the 12-day period and expressed as the average number of accelerations per 5-min intervals (22). Aerobic exercise tolerance (VO2max in ml/min) was estimated using the Åstrand-Rhyming protocol (23). In addition, the distance covered in a six-minute walk test (6MWT) was recorded (24).

MRI ACQUISITION

MRI examinations were performed of the least affected thigh on a 3 Tesla MRI system (TIM Trio, Siemens, Erlangen, Germany) as described previously (15). A fish oil capsule, positioned at one third of the distance between the spina iliaca anterior superior and the patella, served as a landmark for slice matching between the baseline and follow-up measurements. Scout images were acquired in three orthogonal directions to position the MRI slices of the subsequent scans.
The protocol consisted of transversal quantitative T2 multi-slice, multi-spin-echo MR imaging (qT2-MRI) and turbo inversion recovery magnitude (TIRM) imaging with an inversion time (TI) to null fat signals. The qT2-MRI was performed with 16 echo times between 7.7 and 132.2 ms of up to 8 slices with a thickness of 6 mm. The field of view (FOV) was set at 175x175 mm for all scans. To determine the reproducibility of our fat-fraction measurement procedure, the qT2-MRI exam was repeated in eight patients after a minimum of one hour and a maximum of one day after the first measurement.

MRI POST-PROCESSING

The qT2-MR images were analyzed offline with an IDL program (ITT Visual Information Solutions, Boulder, USA, v6.2) developed in-house (14). To compute separate fat and muscle images, the signal intensity of every smoothed pixel was fitted to a bi-exponential function with fixed proton relaxation times for fat (143 ms) and muscle (40 ms). For each muscle, regions of interest (ROI) were carefully drawn on the T2-weighted MR images. ROIs were selected for the rectus femoris

(RF), vastus lateralis (VL), vastus intermedius (VI), vastus medialis (VM), sartorius (S), adductor longus (AL), adductor magnus (AM), gracilis (G), semimembranosus (SM), semitendinosus (ST), biceps femoris long head (BFL) and biceps femoris short head (BFS) (Figure 1). Subsequently, the mean fat-fraction (%) for every ROI was calculated. To assess the reproducibility of the fat-fraction determination the duplicate qT2-MRI acquisitions were subjected to the same procedure.

To ensure that edema would not interfere with the bi-exponential fitting, TIRM images were manually checked for high-intensity zones (MRI signature of edema). Muscles images showing such hyperintense areas were excluded from the qT2-MRI analysis.
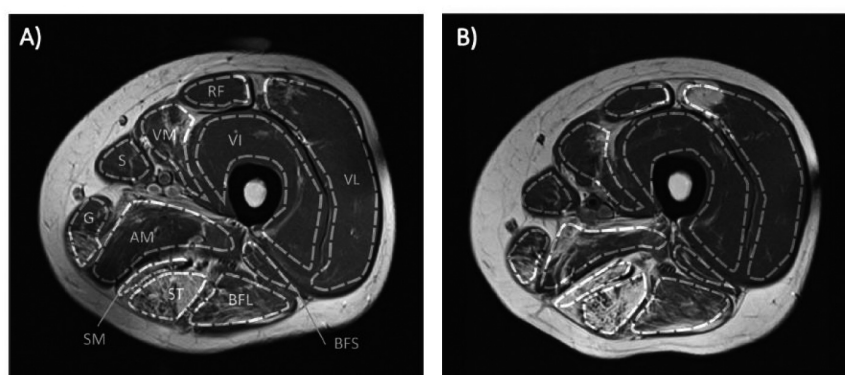
Figure 1 Transversal T2-weighted MR images of the thigh of a 34 year old male FSHD patient receiving usual care, obtained at baseline (A) and at 12-weeks follow-up (B)

AM = adductor magnus; BFL = biceps femoris long head; BFS = biceps femoris short head; G = gracilis; RF = rectus femoris; S = sartorius; SM = semimembranosus; ST = semitendinosus; VI = vastus intermedius; VL = vastus lateralis; VM = vastus medialis. Regions of interest (dashed lines) are drawn on the images of individual muscles to determine muscle-specific fat-fraction. At baseline infiltrated fat is mostly seen in the BFL (30%), G (45%), ST (80%), SM (96%) and AM (16%). The average fat-fraction of the thigh muscles, determined by qT2-MRI, increased from 2% at baseline to 9% at follow-up, but the progression rate depended on the muscle. For example, the fat-fraction of the ST muscle increased by 11% to 91% at follow-up, while no progression was observed in the VI, of which the fat-fraction remained stable at 2%.

STATISTICS

Pearson correlation analyses were performed between fat-fraction of the whole thigh musculature and the physical capacity measures using Prism 5.0 (GraphPad Software, San Diego, California, USA). For the test-retest reliability of the muscle-specific fat-fraction measurements by qT2-MRI, the intraclass correlation coefficient (ICC) was computed (25).

Treatment effects were assessed in two ways. As they are not Gaussian distributed, the average changes in fat-fractions per year in the intervention groups were compared to those obtained for the UC group with one-tailed Mann-Whitney tests (15). A linear mixed model for repeated measurements was used to assess effects on muscle-specific fat-fractions, with treatment (three levels: UC, AET, CBT) as the independent class variable and time (weeks since baseline measurement) and baseline fat-fraction as the independent continuous variable. In addition, interaction terms for treatment x baseline fat-fraction and treatment x time were included. Because we found no statistical significance for the interaction between treatment and baseline fat-fraction, the latter term was omitted from the model. In the UC group, regression per year was calculated using the data of the two measurement points. For the AET and CBT groups, the estimated difference in change per year, with 95% confidence intervals (CI) and corrected for pre-treatment values, was compared to the UC group values. These analyses were performed by using IBM SPSS Statistics for Windows, version 20.0 (IBM Corp, Armonk, New York, USA). Statistical significance was set at $p<0.05$.

RESULTS

SUBJECTS

Of the 57 patients asked to join 44 finally entered the MR study. The main reason for not willing to participate was claustrophobia. Twelve patients were not available for the follow-up MRI measurement (5 for personal reasons and 7 because of logistic problems). The data for one patient was discarded because of movement artifacts in the MR images. Hence, for 31 patients complete datasets were collected, with 13 patients having received UC, 9 AET and 9 CBT. Demographics and clinical characteristics of the patients are presented in Table 1. A Kruskal-Wallis one-way analysis of variance revealed no differences in age and clinical characteristics between the participants and non-participants of the (complete) MRI study.

Table 1 Demographics and baseline characteristics of FSHD patients

	All	NP/NA	MRI			
			All	UC	AET	CBT
Number of patients	57	26	31	13	9	9
Male/female	37/20	15/11	22/9	10/3	7/4	8/3
Age (years)	52±14	50±14	53±14	53±15	56±15	53±12
CSS	2.8±1.0	2.8±1.1	2.8±1.0	3.0±0.9	3.1±1.1	2.3±1.0
Actometer (5 min-1)	39±16	36±16	42±15	43±16	40±16	43±14
6MWT (m)	423±148	416±133	428±167	455±169	386±147	456±190
Fat-fraction (%)	NA	NA	30±35	30±35	32±36	28±36
Adherence (%)	66	60	78	NA	89	67

UC = usual care, AET = aerobic exercise therapy, CBT = cognitive behavioral therapy, CSS = clinical severity score, 6MWT = six-minute walk test, NP/NA = non-participant/not available for MRI study. Except for number of patients and male/female all values are mean ± SD. Acceptable adherence with the AET program was defined as completion of a minimum of 40 training sessions. Acceptable adherence with the CBT program was defined as completion of a minimum of 3 sessions.

BASELINE MRI RESULTS

From the MR images of the thigh of each of the 31 included patients 11 individual muscles were analyzed (Figure 1). In total 341 muscles were analyzed of which 19 muscles showed hyper-intense signals on TIRM images, suggestive of edematous inflammation (Table 2).

Table 2 Number of hyper-intense lesions identified on TIRM MRI for the usual care and intervention groups

	Baseline	Present at baseline and follow-up	New at follow-up	Total at follow-up
UC	8	6	7	13
AET	3	2	0	2
CBT	8	5	2	7

TIRM= Turbo Inversion Recovery Magnitude, UC= usual care, AET= aerobic exercise therapy, CBT= cognitive behavioral therapy.

The analysis of the qT2-MR images revealed that fat-fractions of the remaining muscles (i.e. those with no TIRM lesions) ranged from 2 to100 percent. Some patients presented without any abnormal fatty infiltration of the thigh muscles, whilst others showed severe fatty replacement of specific muscles. The baseline muscular fat-fractions of all patients (average value of all thigh muscles per patient) correlated negatively with the baseline level of physical activity (R^2=0.27, p=0.0013) as measured by the actometer, and with distance walked in the 6MWT (R^2=0.40, p<0.0001), but did not correlate with aerobic capacity (R^2=0.09, p=0.053) (Figure 2). An analysis of the duplicate qT2-MRI data to assess the test-retest performance of the fat-fraction determination yielded an ICC of 0.99
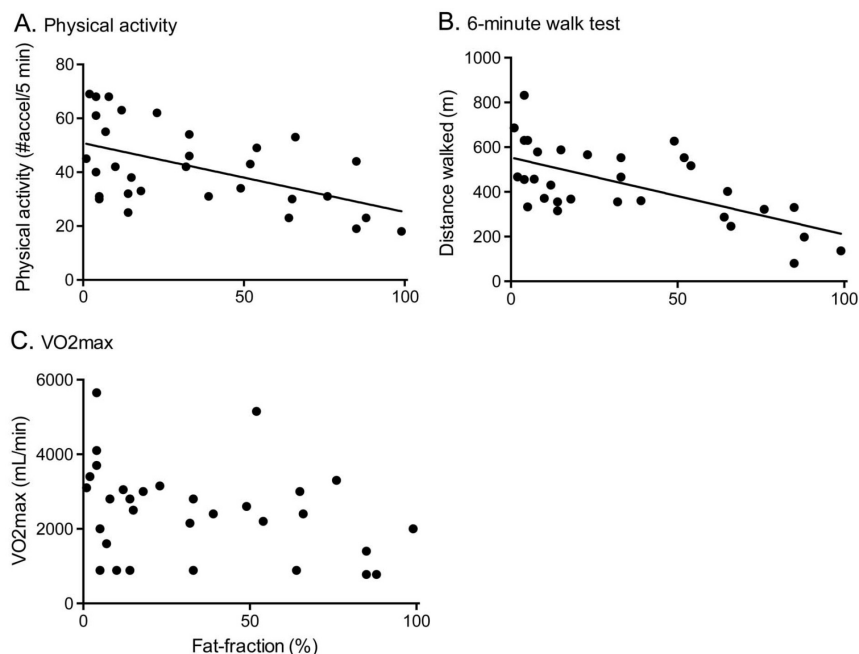
Figure 2 Correlations between fat-fraction, derived by qT2-MRI, in the thigh and common clinical capacity measures of FSHD patients

The average fat-fraction of the whole thigh musculature correlated negatively with physical activity (A) and distance covered in the '6-minute walk test' (B). There was no correlation between the average fat-fraction of the thigh and the peak oxygen uptake (C).

TREATMENT EFFECTS

In the UC group the natural progression of fatty infiltration in all the analyzed thigh muscles was on average 6.7% (95% CI: 4.3% to 9.1%) normalized per year (Figure 3).
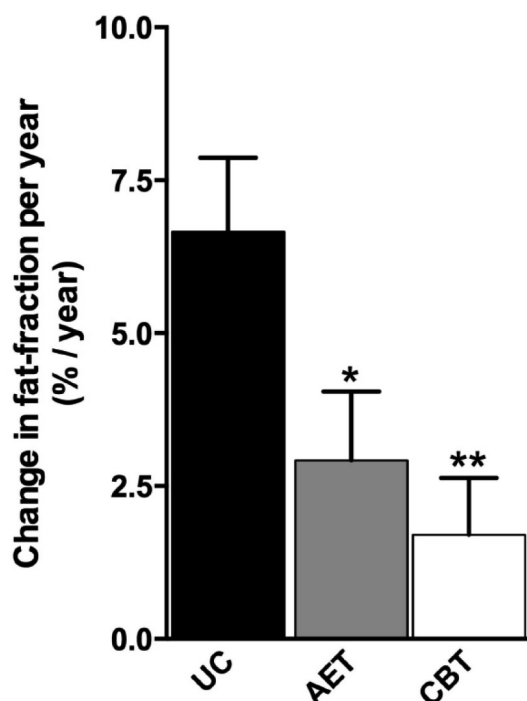
Figure 3 Treatment effects of aerobic exercise training and cognitive behavioral therapy on MRI derived fat-fractions of the individual thigh muscles in FSHD patients

UC = usual care, AET = aerobic exercise training, CBT = cognitive behavioral therapy. Bars indicate the average change in fat-fraction normalized per year for the thigh muscles of FSHD patients receiving no treatment (Usual care), AET or CBT. Values are presented as means±SE. The progression of fatty infiltration was lower for the two treatment groups compared to usual care (* p< 0.05 and ** p< 0.01).

The linear mixed model analysis revealed that for individual muscles an increase in fatty infiltration occurred on average in all muscles except in the G, S and VL. The largest progression was found in the AM with 19% per year (95% CI: 12% to 26%) (Table 3).

Table 3 Intervention effects on the progression of fatty infiltration for individual thigh muscles in FSHD patients

Muscle	Observed fat-fraction (%) for all groups at baseline	Estimated mean fat-fraction extrapolated to one year after baseline (%)						
		UC		AET			CBT		
	Mean (SD)	Mean	(95% CI)	Mean	(95% CI)	P	Mean	(95% CI)	P
AM	38.1 (39.2)	57.1	(49.9 to 64.2)	42.7	(33.2 to 52.2)	0.00	36.5	(26.4 to 46.6)	0.00
BFL	35.2 (38.0)	47.9	(42.7 to 53.2)	34.7	(27.6 to 41.7)	0.00	34.2	(26.7 to 41.7)	0.00
BFS	33.1 (35.7)	42.2	(37.2 to 47.1)	36.4	(29.9 to 43.0)	0.08	31.7	(24.5 to 38.8)	0.01
G	27.7 (37.5)	29.4	(24.5 to 34.3)	27.1	(20.7 to 33.6)	0.48	30.8	(23.8 to 37.8)	0.69
RF	36.2 (37.2)	45.5	(39.1 to 51.9)	37.5	(29.2 to 45.9)	0.06	35.2	(26.0 to 44.4)	0.03
S	19.8 (26.0)	22.0	(17.1 to 26.8)	20.6	(14.3 to 27.0)	0.68	23.5	(16.5 to 30.5)	0.66
SM	54.5 (40.2)	65.8	(59.0 to 72.6)	59.7	(50.7 to 68.7)	0.18	49.9	(40.2 to 59.7)	0.00
ST	41.8 (41.6)	52.7	(48.1 to 57.2)	43.1	(37.1 to 49.1)	0.00	44.1	(37.4 to 50.8)	0.01
VI	14.7 (22.8)	23.9	(20.3 to 27.5)	15.7	(11.0 to 20.4)	0.00	12.6	(7.2 to 18.0)	0.00
VL	13.3 (23.3)	15.2	(12.6 to 17.7)	13.9	(10.6 to 17.2)	0.45	11.5	(7.6 to 15.4)	0.06
VM	19.3 (28.9)	35.2	(31.1 to 39.4)	19.1	(13.7 to 24.5)	0.00	17.8	(11.6 to 23.9)	0.00

UC = usual care, AET = aerobic exercise training, CBT = cognitive behavioral therapy. AM = adductor magnus; BFL = biceps femoris long head; BFS = biceps femoris short head; G = gracilis; RF = rectus femoris; S = sartorius; SM = semimembranosus; ST = semitendinosus; VI = vastus intermedius; VL = vastus lateralis; VM = vastus medialis. A linear mixed model was used to account for repeated measurements. P values refer to a comparison between therapy groups and UC group. Baseline fat-fractions (%) as mean values (SD) and estimated fat-fractions after one year as mean values (95% CI).

In the AET group the average increase in fat-fraction per year was 2.9% (95% CI: 0.7% to 5.2%), which was lower than observed in the UC group (p=0.03) (Figure 3, Figure 4).
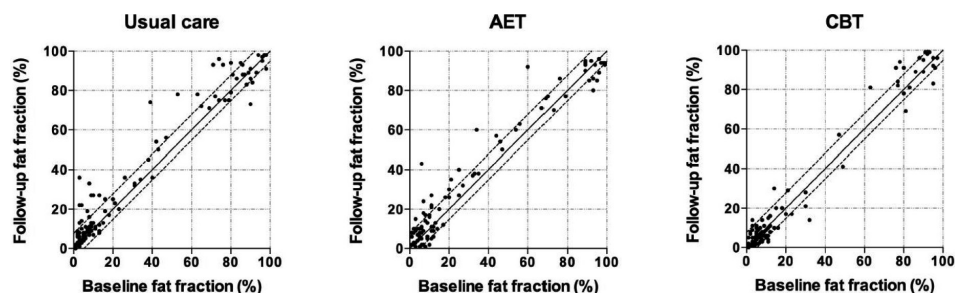

Figure 4 Baseline and follow-up fat-fractions of all individual muscles

AET = aerobic exercise therapy, CBT =cognitive behavioral therapy.
The solid line is the line of unity, if no change in fat fraction would occur all point would be on this line. The dashed line signifies the 95% confidence interval of the fat-fraction determination method. Dots above the unity and upper dashed line indicate muscles in which significant progression has occurred. Note that this is more in the usual care group compared to the intervention groups and that the baseline to follow-up period was shorter in the usual care groups compared to both intervention groups (12 vs 28 weeks).

The individual muscle analyses by a linear mixed model showed significantly less progression of fatty infiltration compared to the UC group in all but the G, S, SM and VL muscles (Table 3). The deceleration of progression of fatty infiltration in the AET group was largest for the VM muscle. In this muscle fatty infiltration did not advance significantly whilst this was obvious in the UC group.

Compared to the UC fat-fraction values, we also computed a lower progression rate for the CBT group: on average 1.7% per year (95% CI: -0.2% to 3.6%) (p=0.0015) (Figure 3). The linear mixed model analyses showed that this deceleration applied to all muscles except for the G, S and VL (Table 3). In this intervention group the effect was largest for the AM muscle. FSHD patients subjected to AET and CBT had fewer new hyper-intense lesions in their muscles on TIRM images than those in the UC group, respectively 2 in 18 and 7 in 13 patients (Table 2), indicating reduced edematous inflammation. Body weight, body mass index and body fat percentage were unaffected by the interventions (Table 4). In both intervention groups, mean registered physical activity increased compared to the UC group. In the AET group, the average number of accelerations per 5-min intervals increased with 2.8 and in the CBT group with 2.9 compared to a decrease of -1.3 in the UC group, adjusted for pre-treatment values.

Table 4 Body weight, body mass index and body fat percentage are not affected by life style intervention in the patients examined by MR

	UC						AET						CBT					
	Baseline		Follow-up				Baseline		Follow-up				Baseline		Follow-up			
	Mean	SD	Mean	SD	diff	p	Mean	SD	Mean	SD	diff	p	Mean	SD	Mean	SD	diff	p
FFMI	17.3	1.3	17.5	1.3	0.2	0.6	19.4	2.5	18.8	2.2	-0.6	0.2	18.0	2.4	17.6	2.2	-0.4	0.2
BF%	28.4	9.4	27.5	10.0	-0.9	0.5	30.5	7.4	32.2	6.9	1.7	0.4	31.3	4.8	32.3	6.0	1.0	0.3
BMI	24.5	3.9	24.5	4.1	0.0	0.8	28.6	4.8	28.2	4.4	-0.4	0.3	26.6	3.4	26.4	3.5	-0.2	0.4
Weight (kg)	79.0	12.2	78.6	12.4	-0.4	0.6	88.6	13.7	87.6	13.4	-1.0	0.4	86.7	16.5	86.3	16.4	-0.4	0.5

UC = usual care, AET = aerobic exercise training, CBT = cognitive behavioral therapy. AM = adductor magnus; BFL = biceps femoris long head; BFS = biceps femoris short head; G = gracilis; RF = rectus femoris; S = sartorius; SM = semimembranosus; ST = semitendinosus; VI = vastus intermedius; VL = vastus lateralis; VM = vastus medialis. A linear mixed model was used to account for repeated measurements. P values refer to a comparison between therapy groups and UC group. Baseline fat-fractions (%) as mean values (SD) and estimated fat-fractions after one year as mean values (95% CI).

DISCUSSION

The main finding of this study is that aerobic exercise therapy (AET) and cognitive behavioral therapy (CBT) directed at optimizing daily physical activity slow down the progression of fatty replacement of muscle tissue in FSHD as evidenced by quantitative T2-MR imaging, demonstrating that the fat-fraction derived by MRI can serve as a sensitive and reproducible biomarker to reveal treatment effects in FSHD. This is clinically relevant as we also demonstrate that fat-fractions correlate with physical activity and distances walked in 6 minutes.

Previously, we proved that muscular fat-fraction determined by qT2-MRI is a sensitive biomarker of disease state in FSHD and that it can detect natural progression in individual muscles within the course of four months (15), whilst leg muscle strength and MR-detected muscle fat infiltration were shown to be strongly correlated (14, 15, 26). With the current qT2-MRI study we substantiate that both AET and CBT interventions significantly decelerate disease progression as reflected in the fatty infiltration of thigh muscles within a time span of four months. Our muscle-specific linear mixed model analyses show that treatment effects are not the same for all muscles. For instance, retardation of fatty infiltration is most pronounced in the adductor magnus and vastus medialis but absent in the gracilis, sartorius and vastus lateralis muscles. This difference can be explained by the insignificant fatty progression rates for the latter muscles in the usual care group across the trial period. A decreased fat infiltration rate was also detected in two leg muscles of boys with Duchenne muscular dystrophy due to corticosteroid therapy by determining fat-fractions with single voxel MR spectroscopy (27).

In the absence of a causal treatment for FSHD it is important to find approaches that slow down disease progression (28). Of the studies exploring pharmacological and non-pharmacological interventions (7, 8, 10, 28-35), until recently only some physical therapy programs showed a beneficial effect, while their application remained controversial due to the lack of controlled studies (28). We recently reported in an RCT that both AET and CBT significantly reduce chronic fatigue in FSHD patients as assessed with the Checklist Individual Strength (CIS-fatigue). In another RCT from a different group, physical fitness, workload and walking speed improved after 12 weeks of AET (8). However, a positive effect on the muscular level has never been described before (7-10). In the present study, using the fat-fractions derived from qT2-MR imaging, we were able to demonstrate significant treatment effects, from which we infer that determining fatty infiltration volumes in skeletal muscles is a more sensitive instrument than the mentioned physical

capacity measures. The higher sensitivity and reproducibility of fat-fractions obtained by qT2-MRI compared to muscle strength measurements in intervention trials (36) can be explained by confounding practicalities of the latter method such as influence of limb position, motivation and placebo effects (9) and also because entire muscle groups are gauged, thus obscuring effects on individual muscles. The similar positive effects of AET and CBT on the rate of muscle fat infiltration is understandable as both interventions aimed to increase the level of physical activity: AET by three-weekly cycling exercises and CBT by a daily physical activity program consisting of graded increased cycling or walking exercises. Indeed, both AET and CBT increased the level of daily activity, as objectively measured by accelerometry (7). The particular physical activity programs may well explain the positive effect of both therapies on fatty infiltration of the upper leg muscles as these muscles are essential for walking and even more so for cycling. This indicates that adopting an overall active lifestyle by an increased level of physical activity of sufficient duration slows down the progression of fatty replacement of muscle tissue in patients with FSHD by an underlying mechanism common for both interventions. In future studies it will be of interest to include qT2-MRI in more detailed investigations of the levels of physical activity required to obtain beneficial effects in these patients.

Some aspects need to be taken into account in the interpretation of the results. A selection bias may have occurred in the specific recruitment of the patients for the MR study. However, as there were no significant differences in patient characteristics and physical capacities between the 31 patients participating in the MR study and the 26 non-participants, a selection bias is not expected to be relevant. To correct for the timing difference between the baseline and follow-up measurement of the control and intervention groups we normalized the change in fat-fractions for all groups to one year. This assumes linear progression of fatty infiltration in all groups, which might not reflect its true course. Because the interval between the two MR measurements was longer in the intervention groups than in the usual care group there is more time for a potential increase in fatty infiltration in these intervention groups, in particular during the usual care period inserted before the follow-up MR measurement. Hence, it is unlikely that the deceleration of fatty infiltration by the interventions is positively biased by the normalization procedure.

Exercise enhances several capacities that will lead to stronger muscles and less fatigue, but may also provide favorable conditions to slow down progression of muscle affliction and to regenerate muscles in neuromuscular disorders (37, 38). A primary role in the pathophysiology of FSHD has been suggested for a DUX4

induced immune response (39). This is in agreement with the observation of hyper-intense signals in TIRM or STIR MR images of muscles in patients, which are indicative of edematous inflammation (2, 14, 39). The MR signatures for these processes are particularly relevant as they seem to indicate that edema may precede the process of fatty infiltration (15-17). Therefore, it is of interest that both intervention groups showed less new hyper-intense lesions at follow-up.

In this study we demonstrate that the rate of fatty infiltration as determined by qT2-MRI in individual muscles of patients with FSHD is significantly decelerated after AET and CBT compared to usual care. We also show that this MRI approach is reproducible and can be used to obtain direct, sensitive and objective measures for the muscular state in legs of FSHD patients.

These results reinforce the notion that quantitative MRI may become an indispensible endpoint in clinical trials for muscular dystrophies (40).

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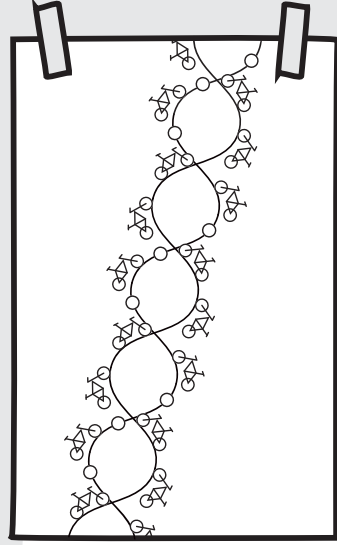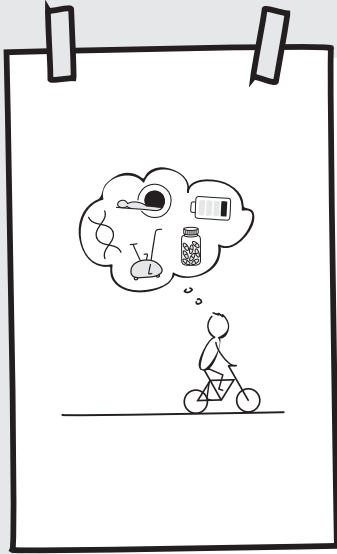
CHAPTER 9

SUMMARY AND GENERAL DISCUSSION

SUMMARY

Facioscapulohumeral muscular dystrophy (FSHD) is the third most common muscular dystrophy worldwide with an estimated prevalence of one in 8,000 persons. It is an autosomal dominant disorder affecting primarily the muscles of the face and the shoulder girdle, but later in life many muscles of the trunk and the extremities can become affected. In the last decade, substantial progress has been made in the understanding of the molecular genetics of FSHD. More than 95% of the cases of FSHD are associated with a partial deletion of a critical number of repetitive elements (D4Z4) on chromosome 4q35 and the subsequent toxic release of the DUX4 protein in muscle cells. It is, nevertheless, still unknown why the weakening of different muscles and muscle groups occurs at different rates and times. Moreover, there are no biomarkers for an objective assessment of the severity and progression of FSHD.

To date, no curative treatment is available for FSHD. As a consequence, although life expectancy is normal, 20% of the patients become wheelchair-bound due to muscle weakness. In addition, more than 60% of the patients experience chronic fatigue and with that, a lower level of social participation. Physical inactivity has shown to be the most important perpetuating factor of fatigue in patients with FSHD. However, being physically active is difficult for patients because of muscle weakness, which may lead to a vicious circle of fatigue and inactivity.

The two main aims of this thesis were (1) to study the issues of fatigue and (in)activity in neuromuscular disorders and (2) to evaluate the effect of model-based interventions to optimize the activity level and reduce chronic fatigue in FSHD.

Chapter 1 is the general introduction and provided background information on FSHD. Individuals with FSHD show a wide range of clinical manifestations. This variability suggests that epigenetic mechanisms play an essential role. Epigenetics is defined as heritable changes in gene activity and expression that occur without alteration in DNA sequence. To objectively assess the severity and progression of FSHD, magnetic resonance imaging (MRI), could provide an objective biomarker for individual muscle involvement as it can easily visualize intramuscular fibrosis and fatty infiltration. Fatigue is increasingly being recognized as a major clinical problem in many conditions and evidence-based treatment programs are now being developed for several patient groups. By using the subscale fatigue of the Checklist Individual Strength, a multidimensional fatigue scale, it appeared that more than 60% of the patients with FSHD were severely fatigued. Lack of physical activity, sleep disturbances and pain contributed to experienced fatigue in FSHD. Loss of muscle strength contributed to experienced fatigue through a lower level of physical activity. This model of perpetuating factors served as a basis for the

treatment protocol used in this thesis. This thesis reports the results of the FACTS-2-FSHD study (acronym for Fitness And Cognitive behavioral TherapieS for Fatigue and ACTivitieS in FSHD), which is the first model-based randomized clinical trial that evaluated the effects of aerobic exercise training (AET) and cognitive behavioral therapy (CBT) on chronic fatigue in patients with FSHD.

It was hypothesized that, in order to alleviate chronic fatigue, two different therapeutic approaches could be followed: AET to promote physical activity and CBT to stimulate an active lifestyle (yet avoiding excessive physical strain). Hence, the primary objective of this study was to evaluate the effect of both interventions on chronic fatigue in patients with FSHD as assessed with the subscale fatigue of the Checklist Individual Strength. The secondary objective was to evaluate the effects of each intervention on the known perpetuating factors of chronic fatigue in FSHD.

The secondary outcome measures covered all domains of the International Classification of Functioning, Disability and Health (ICF). In addition, it was aimed to find clinically useful magnetic resonance imaging (MRI) biomarkers of disease progression and response to therapy in patients with FSHD.

PART 1: PREVALENCE, ETIOLOGY, ASSESSMENT AND MANAGEMENT OF FATIGUE

In part 1, an overview is provided of the prevalence, assessment, and treatment of fatigue in neuromuscular disorders. The following research questions are addressed:

1. What is the prevalence and relevance of fatigue in patients with muscular dystrophy?

🚲 **Chapter 2** shows that fatigue is a frequent and relevant symptom in patients with muscular dystrophy. Distinguishing experienced fatigue from muscle weakness, the key feature in muscular dystrophy, may be difficult. Although experienced fatigue is difficult to define, it still is a valuable concept which can be reliably measured by using questionnaires, like the Checklist Individual Strength, subscale fatigue (CIS-fatigue). As fatigue in muscular dystrophy is a multidimensional concept, it is important to understand factors that contribute to fatigue. Based on such an analysis, preventive and therapeutic interventions could be developed. Therefore, an overview of the pathophysiological determinants of fatigue in muscular dystrophies was provided and the model of perpetuating factors of experienced fatigue in FSHD was presented. A critical overview of the possible treatment options with respect to fatigue in patients

with muscular dystrophy was presented including physical exercise training, drug treatment and cognitive behavioral therapy.

2. How can we assess fatigue in patients with neuromuscular disorders?

🚲 **Chapter 3** describes the results of a European Neuromuscular Centre (ENMC) care Workshop regarding pain and fatigue in neuromuscular disorders (NMD). This workshop aimed to achieve consensus on the definitions of pain and fatigue in NMD and to define a core set of measurement instruments for pain and fatigue in this group of disorders. Pain as well as fatigue are common symptoms in NMD with a strong impact on many activities of daily life. Specific types of pain and fatigue, related to the underlying (stages of) NMD could be distinguished. These should be differentiated from aspecific pain and fatigue, which are not primary related to the underlying disorder. Various methods were being used to assess pain and fatigue in NMD. In order to develop effective treatment approaches in NMD, both the definitions of pain and fatigue and their assessment methods should be internationally agreed upon. Therefore, a core set of measurement instruments for use in future research and clinical practice in NMD was provided.

3. What is the evidence for exercise in muscle disease?

🚲 In **chapter 4**, an updated Cochrane review (most recent date of search 2 July 2012) is presented on the safety and efficacy of strength training and aerobic exercise training in people with a muscle disease. Strength training or aerobic exercise programs might optimize muscle and cardiorespiratory function and prevent additional disuse atrophy and deconditioning in people with a muscle disease. All randomized or quasi-randomized controlled trials comparing strength training or aerobic exercise programs (or both) to no training, lasting at least six weeks, in people with a well-described diagnosis of a muscle disease were included. Five eligible trials with 170 participants fulfilled the inclusion criteria: two trials of strength training in people with FSHD and myotonic dystrophy (101 participants), two trials of strength training combined with aerobic exercise in people with mitochondrial myopathy (18 participants) and myotonic dystrophy type 1 (35 participants), and one trial of aerobic exercise in people with polymyositis and dermatomyositis (14 participants). These trials showed that moderate-intensity strength training in people with myotonic dystrophy or FSHD, and aerobic exercise training in people with dermatomyositis or polymyositis appeared not to harm muscles. Strength training combined with aerobic exercise appeared to be safe in myotonic

dystrophy type 1 and might be effective in increasing physical endurance in people with mitochondrial myopathy. Finally, strength training was not harmful in people with FSHD, myotonic dystrophy, mitochondrial disorders or dermatomyositis / polymyositis, but there was insufficient evidence to determine its potential benefit. Limitations in the design of studies in other muscle diseases prevented more general conclusions.

PART 2: THE FACTS-2-FSHD STUDY

In part 2, the results of the FACTS-2-FSHD study are presented. The following research questions are addressed:

4. What are the effects of aerobic exercise therapy and cognitive behavioral therapy on chronic fatigue in patients with FSHD?

In **chapter 5** the protocol of the FACTS-2-FSHD trial is described. The FACTS-2-FSHD study was the first theory-based randomized clinical trial which evaluated the effect and the maintenance of effects of AET and CBT on the reduction of chronic fatigue in patients with FSHD. The interventions were based on a theoretical model of perpetuating factors of chronic fatigue in patients with FSHD. The primary objective of the FACTS-2-FSHD trial was to study the efficacy of AET and CBT for decreasing chronic fatigue in patients with FSHD type 1 compared to usual care. It was hypothesized that both AET and CBT would be more effective in decreasing fatigue than usual care, which is no therapy at all or occasional (conventional) physical therapy. The improvement by AET might be obtained through enhancement of physical (aerobic) capacity, whereas beneficial effects of CBT might be achieved through changes in daily activities and behavior. Secondary objectives were to evaluate the effects of AET and CBT on the known fatigue-perpetuating factors in FSHD. The AET consisted of aerobic cycling exercise on a bicycle ergometer. The training program had a duration of 16 weeks and comprised home training twice a week and a supervised training once a week. CBT was focused on all known perpetuating factors of fatigue and adapted to the needs of each patient. Each session had a duration of one hour and was given by a registered cognitive behavioral therapist. At baseline, patients were randomized to either an AET group, a CBT group, or a control group receiving usual care. After an intervention period of 16 weeks and a follow-up of 3 months, the control group was as yet randomized to either AET or CBT (28 weeks after inclusion). It was intended to eventually include 25 adult patients in each of the three groups: AET, CBT, or usual care. Because patients in the control group received AET

or CBT in second instance, the minimal number of patients to be included was 50 at baseline. Outcomes were assessed at baseline, immediately post intervention (and control period), and at 12 en 24 weeks of follow-up. A linear mixed model for repeated measurements was used to study the estimated group differences.

Chapter 6 describes the results of the FACTS-2-FSHD randomized controlled trial for which the protocol has been described in **chapter 5**. Fifty-seven ambulant patients with FSHD type 1 and severe chronic fatigue were randomly allocated to AET, CBT, or UC. Following treatment, both the AET (28 participants) and CBT (25 participants) intervention groups had significantly less fatigue relative to the UC group (24 participants), with a difference of -9.1 for AET (95% CI: -12.4 to -5.8) and -13.3 for CBT (95% CI: -16.5 to -10.2) on the CIS-fatigue. These beneficial effects lasted through follow-up, with a difference of -8.2 for AET (95% CI: -12.4 to -5.8) and -10.2 for CBT (95% CI -14.0 to -6.3). Post-treatment, 19 participants in the CBT group (76%) and 14 participants in the AET group (50%) no longer had scores indicative of severe fatigue. The number needed to treat (NNT) for AET was 2.3 (95% CI 1.4– 3.1) with an absolute risk reduction (ARR) of 50% (95% CI 32–69%). The NNT for CBT was 1.3 (95% CI 1.1–1.7) with an ARR of 76% (95% CI 59–93%). In the CBT group, all known fatigue-perpetuating factors (with the exception of pain) were positively modified, including a higher level of social participation. The patients who received AET showed an increase in registered physical activity and maximal isometric quadriceps strength only. The increase in registered physical activity in both groups and the improvement in social participation following CBT were still present at follow-up. More than 70% of the AET and almost 80% of the CBT participants continued their adjusted level of activity once the study had ended. No improvement in aerobic capacity was found in both intervention groups. Only mild adverse affects were found in the AET group. The median number of therapy sessions was much lower in the CBT group, i.e. five, than in the AET group (40 sessions). It was concluded that both AET and CBT are able to ameliorate chronic fatigue in patients with FSHD.

5. Can we discover structural abnormalities in skeletal muscle of FSHD patients that may serve as biomarkers for disease progression and response to therapy?

Even though the most important genetic event for the disease has been identified, the underlying mechanisms causing FSHD are unknown. Understanding these mechanisms first requires a better knowledge of the process of fatty infiltration of the skeletal muscles.

In the study described in **chapter 7**, fat fraction as assessed by quantitative MRI (Q-MRI) appeared to be an objective and sensitive biomarker for muscular affliction in FSHD, detecting even subclinical muscle involvement. An analysis of the average fat fraction for all individual muscles uncovered an hourglass pattern of many muscles with either a very low or high fat fraction, and few muscles with an intermediate fat fraction. This quasi-binary distribution had not been reported for other muscular dystrophies and may be FSHD specific. The intramuscular fat fraction increased linearly from proximal to distal. Fat replacement of entire muscles would, on the average, be completed within approximately three and a half years. The steepest fat gradient occurred in the intermediately affected muscles indicating that these muscles were quickly progressing towards a complete fat infiltrated state. This can be relevant for prognostication and monitoring therapy effectiveness in FSHD.

The primary goal of the study presented in **chapter 8** was to examine the effects of AET and CBT on the progression of fatty infiltration and edema in individual leg muscles of FSHD type 1 patients by T2-MRI. Quantitative T2-MRI (qT2-MRI) and fat-suppressed T2-MRI images of the thigh were obtained at baseline and follow-up in 31 patients who were included in the FACTS-2-FSHD study, of whom 13 received usual care (UC), nine AET, and nine CBT. In the UC group the fatty infiltration in the affected muscles progressed on average with 6.7% per year. Progression occurred on average in all muscles except in the gastrocnemius, sartorius and vastus lateralis. Overall, the adductor magnus showed the largest progression. This rate was significantly lowered by both interventions to (on average) 2.9% per year in the AET group (AET – UC, $p<0.05$) and 1.7% per year in the CBT group (CBT – UC, $p<0.01$). In both intervention groups fewer muscles developed edema than was observed in the UC group. The baseline muscular fat fractions of all patients (average value of all thigh muscles per patient) were negatively correlated with the baseline level of physical activity ($R^2=0.27$, $p=0.0013$) as measured by the actometer and with the maximum walking distance ($R^2=0.40$, $p<0.0001$), but they were not significantly correlated with aerobic capacity. It was concluded that qT2-MRI is a reproducible and sensitive quantitative biomarker for monitoring the effects of increased physical activity in individual muscles in FSHD and that both AET and CBT slow down the progression of fatty replacement of muscle tissue in FSHD.

GENERAL DISCUSSION

Mr. C, a 58-year old man with facioscapulohumeral dystrophy (FSHD) who was briefly introduced in the general introduction of this thesis, was encouraged by his wife to take part in the FACTS-2-FSHD study, hoping to achieve a reduction of his fatigue. He hoped to be randomized to aerobic exercise training to resume his cycling exercises. He had given up those exercises a couple of years ago for fear of further deterioration of his muscle strength. However, in the study he was randomized to cognitive behavioral therapy (CBT). Initially he was disappointed, as he did not really want to talk to a psychologist about his muscle disease and the burden of his disease. During the study, he received nine sessions of CBT. In the beginning, he was skeptical about this treatment, and therefore did not expect CBT to have any effect. He regarded his experienced fatigue as an untreatable problem. Several measurements that were conducted during the first treatment session with the psychologist showed that the CBT should be directed at unhelpful thoughts and beliefs about fatigue, improper coping strategies, sleep disturbances, physical inactivity and unhelpful social interactions. After nine sessions of CBT and homework assignments, his physical activity had increased substantially. Together with his partner, he went out on an electric bike again to visit his family and friends. He was no longer afraid of muscle damage from physical activity because he noticed that he felt more fit by being physically active. He resumed his gardening activities, this time in the communal garden of the apartment complex where he lived. He no longer slept during lunchtime, so the quality of sleep at night became better. He was not seriously fatigued any more. His mental and physical capacity increased, and there was room for new activities. A few weeks after the end of the CBT, he started a new job.

A MODEL-BASED TRIAL

The Departments of Neurology, Rehabilitation and Pediatrics of the Radboud University Medical Center together with the Expert Center for Chronic Fatigue collaborate in the Center of Expertise for Muscular Dystrophy and have worked together in research and patient care in muscular dystrophy for over 20 years. One of the research successes is the result of cross-sectional and longitudinal research on experienced fatigue in facioscapulohumeral dystrophy (FSHD). Cross-sectional research showed that experienced fatigue is a frequent as well as a relevant problem for patients with FSHD. Based on longitudinal data, a model of perpetuating factors of experienced fatigue in patients with FSHD was developed (1). Muscle weakness, the key feature of FSHD and the result of fatty infiltration

of the skeletal muscles, appeared to contribute only indirectly to experienced fatigue. However, muscle weakness leads to physical inactivity, the most important perpetuating factor of experienced fatigue. Sleep disorders and pain are the other proven perpetuating factors of experienced fatigue. This FSHD-specific model was of major importance for the development of the evidence-based interventions in the FACTS-2-FSHD study, namely aerobic exercise training (AET), aimed at increasing aerobic capacity, and cognitive behavioral therapy (CBT), a psychological treatment aimed at promoting a physically active lifestyle (1) (Figure 1).
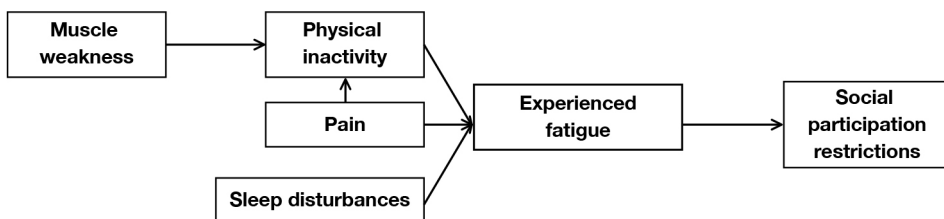
Figure 1 Model of perpetuating factors of experienced fatigue, specifically for patients with facioscapulohumeral dystrophy

Physical inactivity, sleep disturbances and pain are direct and muscle weakness is an indirect perpetuating factor of experienced fatigue (1).

Both interventions in the study are directed at the aforementioned perpetuating factors of experienced fatigue. AET focuses primarily on the perpetuating factor of physical inactivity. This was expected to reduce the chronic experienced fatigue and enhance the degree of social participation. It was hypothesized that an increase in aerobic capacity could lead to a lower level of experienced fatigue (Figure 2).

Cognitive behavioral therapy (CBT) is composed of six modules directed at the proven and presumed perpetuating factors of experienced fatigue and their related (unhelpful) cognitions in FSHD. The modules focus on: (1) unhelpful coping strategies; (2) unhelpful cognitions about fatigue; activity, pain or other symptoms; (3) catastrophic thoughts about fatigue; (4) sleep disturbances; (5) physical inactivity or dysregulation of physical activity; and (6) a discrepancy between expected and actual social support and interactions. Additionally, reducing restrictions in social participation is an important objective of the CBT. In this way, the final aim is to reduce chronic fatigue and social participation restrictions (Figure 3).

Figure 2 The expected working mechanism of aerobic exercise training (AET) based on a model of perpetuating factors of experienced fatigue in patients with facioscapulohumeral dystrophy (Figure 1)

AET focuses primarily on the perpetuating factor physical inactivity. Improved physical activity would diminish the level of experienced fatigue and social participation restrictions.
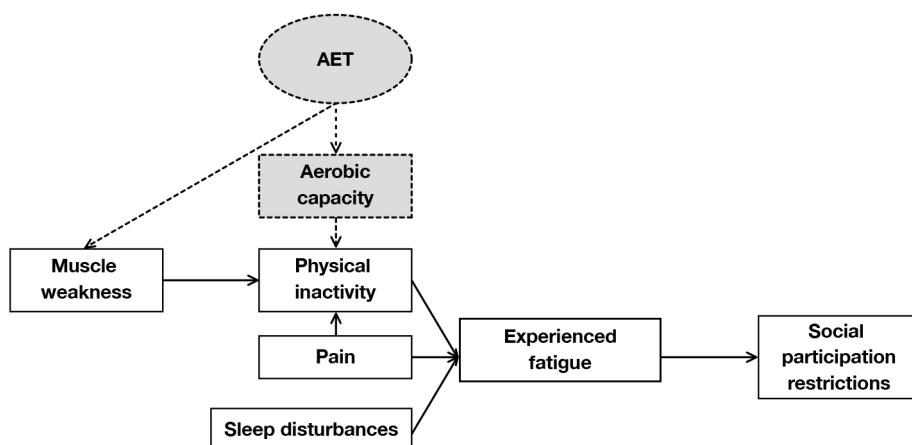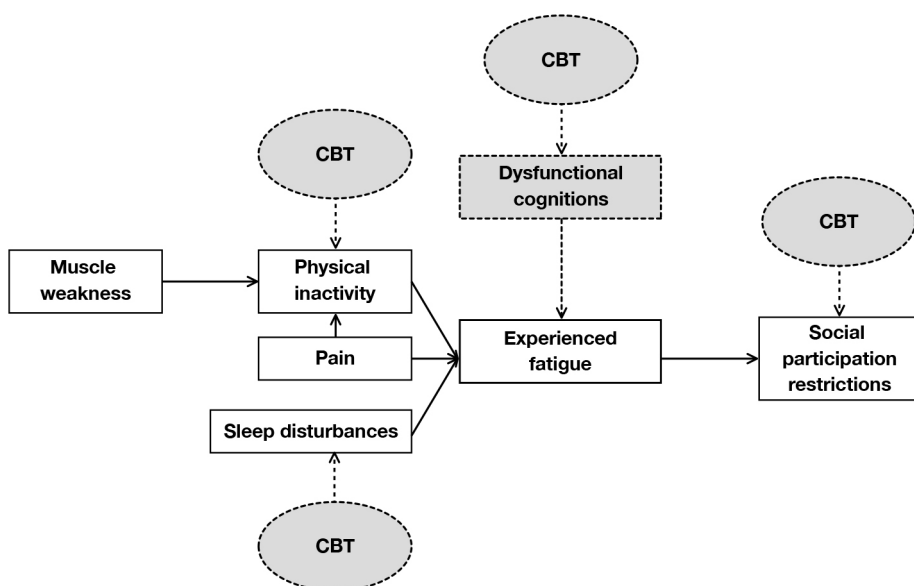

Figure 3 The expected working mechanism of cognitive behavioral therapy (CBT) based on a model of perpetuating factors of experienced fatigue in patients with facioscapulohumeral dystrophy (Figure 1)

CBT focuses not only on the perpetuating factor physical inactivity, but also on sleep disturbances, pain, unhelpful cognitions about fatigue and restrictions in social participation.

The patient with FSHD described in the case study showed an improvement in all domains of the International Classification of Functioning, Disability and Health after only nine sessions of CBT (2). Not only did he experience a lower level of fatigue and an improvement in sleep quality, he also became more physically active. He performed gardening activities again, his social contacts increased and he started a new job. CBT broke the downward spiral of physical inactivity, experienced fatigue and social participation restrictions.
He became physically active in daily life, and social participation became possible again.

The case study illustrates the general conclusion of this thesis: CBT is able to reduce severe fatigue in patients with FSHD and improve social participation, by increasing physical activity and changing all relevant fatigue perpetuating factors (Figure 3).

In addition, the FACTS-2-FSHD study shows that AET can also achieve a reduction of severe chronic fatigue and increase in physical activity in patients with FSHD (Figure 2). Although AET, contrary to CBT, did not cause an improved quality of sleep or social participation, it did cause an increase in muscle strength of the quadriceps. Finally, a deceleration of fatty replacement of muscle tissue in the thigh muscles was observed after both interventions.

POSSIBLE EXPLANATIONS FOR EFFECTS: A PHYSICALLY ACTIVE LIFESTYLE VERSUS PHYSICAL EXERCISE

Physical inactivity

After both CBT and AET, the level of physical activity in daily life increased. After CBT, the level of physical activity remained high compared with the control group, even after the follow-up period of 12 weeks. The increase in physical activity in everyday life appears to play an important role in the positive effect of both interventions on the level of fatigue. Based on the model of perpetuating factors of fatigue and additional research, it is known that in FSHD the degree of fatigue is not correlated with the severity of muscle weakness (1, 3). Apparently, this fatigue seems more a result of unintentional unhelpful behavior associated with the disease rather than the result of muscle weakness itself. Conversely, experienced fatigue often leads to unhelpful cognitions and behavior that, in turn, further increase the level of fatigue. A curative treatment for FSHD is not available yet; however, a treatment aimed at the aforementioned unhelpful cognitions and behavior, namely CBT and AET, now is.

A physically active lifestyle versus physical exercise: 'Dutch standard for healthy exercise' versus ' the standard for physical fitness'

During CBT, a reliable increase in physical activity is an important part of the treatment: the module 'physical-inactivity or a high dysregulation of activity' was applied in each participant. AET focused primarily on physical exercise on an ergometer. At first sight, physical activity and physical exercise seem to be similar, but on second thought they are substantially different. Physical activity is defined as "any effort of skeletal muscles resulting in higher energy consumption than in resting conditions (4)." Physical (aerobic) exercise is a form of physical activity and is defined as "planned, structured and repetitive exercises with an increasing magnitude and intensity in order to maintain or improve physical fitness or aerobic capacity (4)."

The recommendations on physical activity for the healthy population have been prescribed in the Dutch Standard for Healthy Exercise (Nederlandse Norm Gezond Bewegen; NNGB). This standard aims at a physically active lifestyle and comprises a total of 30 minutes of exercise of moderate intensity (at a slightly higher heart and respiration rate than usual) of at least 4.0 MET a day, in blocks of at least 10 minutes at least five days a week.

The MET value or the metabolic equivalent is a unit of measurement within physiology expressing the amount of energy for a certain physical effort compared with the amount of energy required at rest. One MET corresponds to the resting metabolic rate, the amount of energy consumed during inactivity. One MET is equivalent to 3.5 ml of oxygen per kg of body weight per minute. The NNGB leads to a total duration of 150 minutes of physical activity per week of 4.0 MET, which implies a total increase of 450 MET per week compared to a physically inactive lifestyle. Physical activity within the NNGB includes not only sports activities but also daily-life activities such as household activities, cycling or walking the dog.

For physical exercise, the Dutch government has issued a standard for physical fitness. This standard is aimed primarily at maintaining aerobic capacity through physical exercise and requires intense physical activity of at least 6.0 MET for at least 20 minutes and at least three times a week. Although the intensity is higher than in the NNGB, the total length and the increase in MET per week is less, namely 300 MET. Thus, one can still have a physically inactive or sedentary lifestyle, in spite of meeting the standard for physical fitness. In other words, the NNGB leads to a higher level of physical activity than the Dutch standard for physical fitness.

The Dutch standard for physical fitness and the NNGB are defined only for healthy adults and for healthy elderly. The minimum standard for patients with a chronic disease, including FSHD, has not yet been defined. The NNGB not only leads to a higher level of physical activity; this standard is probably also more feasible for patients with FSHD, because daily-life activities are included. In other progressive neurological diseases, such as Parkinson's disease, there is already growing evidence for a positive effect of decreasing the sedentary time (5). The question now arises whether physical exercise of minimum intensity and an increase in aerobic capacity are really necessary for the treatment of fatigue in patients with FSHD. Would an increase in physical activity of moderate intensity and of sufficient duration, i.e. a physically active lifestyle, not be much more relevant?

In order to answer this question, possible underlying mechanisms of the results of the FACTS-2-FSHD study will be discusses. The results of the FACTS-2-FSHD study will be compared with other exercise studies in FSHD and other neuromuscular disorders (NMDs). The methodological limitations will be highlighted and, finally, recommendations will be given for future research and clinical practice.

UNDERLYING MECHANISMS OF EFFECTS

Aerobic exercise: is an increase in aerobic capacity necessary?

In the FACTS-2-FSHD study, the primary purpose of AET was to treat fatigue in patients with FSHD through physical exercise on an ergometer. The hypothesis was that such exercise would improve aerobic capacity and, with that, break the downward spiral of physical inactivity and fatigue (Figure 2). Indeed, the downward spiral was broken: the level of physical activity increased after AET, and the level of experienced fatigue decreased.
However, contrary to our expectations, we found no effect on aerobic capacity. Unfortunately, with the results of the FACTS-2-FSHD study, a real absence of effect cannot be determined with certainty. The Åstrand submaximal cycling test appeared to be unfeasible for relatively severely affected patients. Further considerations will be discusses in the Methodological Considerations paragraph (see page 233).

The results of the FACTS-2-FSHD study suggest that an increase in aerobic capacity is not essential for the reduction of chronic fatigue. Possibly promoting physical activity through physical exercise is a more important mechanism.

Cognitive behavioral therapy:
FSHD is more than impaired muscle function

Where AET aims at improving physical activity, CBT is aimed at all perpetuating factors of the model of Kalkman (Figure 3). This could explain why CBT had a lasting positive effect not only on physical activity but also on sleep quality and social participation. The CBT intervention was more extensive than AET. The treatment protocol of CBT consisted of six modules based on the proven and presumed perpetuating factors of experienced fatigue in patients with FSHD. The modules aimed to change unhelpful disease cognitions, to better regulate social activities, to increase mental activities and to regulate social support. In the first treatment session, the psychologist determined which modules were applicable by performing an interview and specific tests. Thus, compared with AET, CBT was more focused on the individual person with FSHD. In the longitudinal study in which the model of perpetuating factors of experienced fatigue has been developed, only a limited number of possible perpetuating factors could be explored (1). The sample size was too small to reliably test more factors. Therefore, one or more of the presumed perpetuating factors of experienced fatigue (discrepancy in the level of perceived social support, unhelpful illness cognitions and limited social and mental activities) could also be perpetuating factors of experienced fatigue in patients with FSHD. For example, unhelpful illness cognitions are a known perpetuating factor of experienced fatigue in multiple sclerosis and in chronic fatigue syndrome (6). As an essential part of CBT, unhelpful cognitions can be changed into helpful thoughts using Socratic dialogues to increase patients' autonomy and self-efficacy.

Although increasing the amount of physical activity is an essential part of CBT for Although increasing the amount of physical activity is an essential part of CBT for fatigue in FSHD, both scientists and clinicians are astonished about its beneficial effect. "Is fatigue all in the mind?" and "How can a psychological treatment achieve an effect at a muscular level?" are frequently asked questions. The answer to these questions is that a part of the solution is, in fact, literally "in the mind."Psychological factors, such as illness cognitions, coping style and level of acceptance of the disease are known to be strongly correlated with the degree of social participation in patients with a muscle disease, including FSHD (7). It is noteworthy that these correlations, comparable with the level of experienced fatigue, are relatively independent of the degree of physical impairments. This is also called the "disability paradox:" having physical impairments has little influence on the degree of social participation.

This paradox can be explained by the perceived burden of disease in patients with FSHD (Figure 4). As shown in Figure 4, muscle weakness is not only just an indirect perpetuating factor of experienced fatigue, it also constitutes a relatively small part of the experienced burden of disease. Fatigue, pain, sleep disorders and physical inactivity determine the majority of the experienced burden of disease in FSHD. This implies that psychological interventions are not only able to improve the level of experienced fatigue, but can also improve the degree of social participation and mood of patients with a muscle disease, even when there is progression of the disease (8).

Physical inactivity

Sleep disturbances

Pain

Fatigue

Muscle weakness
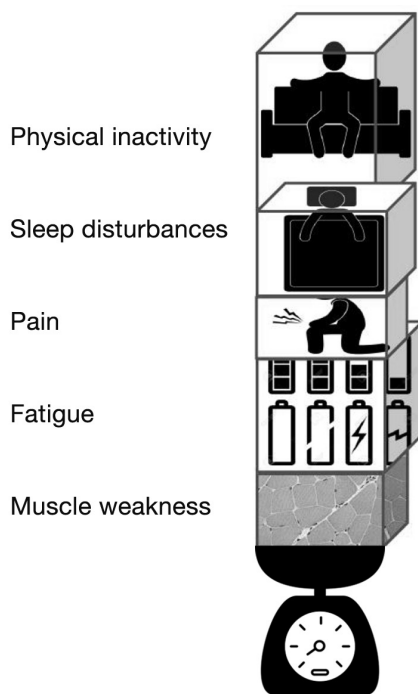
Figure 4 The imaginative tower of experienced burden of disease in patients with facioscapulohumeral dystrophy

FSHD is more than impaired muscle function. A large part of the experienced burden of disease consists of the proven perpetuating factors of fatigue. Not every factor carries equal weight. Experienced fatigue and physical inactivity constitute the main part of the disease burden. The figure is a visual representation of the results of the study by Johnson et al (9).

The disability paradox seems to explain part of the large observed effects of CBT. Psychological well-being improved after CBT, as measured by the Brief Symptom Inventory (10) (unpublished data), and the level of social participation increased.

This occurred independent of a change in muscle strength, which is often used as a measure of disease severity. For many patients, psychological distress is, together with a decrease in muscle strength, a significant problem. Stress, fear for the future, and fear for fatigue were frequently mentioned in the parallel qualitative FACTS-2-PERSPECTIVES study during the interviews before the start of the intervention (11, 12).

Effects at the muscular level: epigenetics and/or anti-inflammatory effects?

Both CBT and AET slow down the progression of fatty replacement of muscle tissue in FSHD. This raises the question: "How is it possible that an increase in physical activity causes a beneficial effect at the muscular level?" Epigenetics and the inflammation theory can possibly offer an explanation.

Epigenetics

FSHD is a genetic disorder. More than 95% of cases of FSHD are associated with the absence of certain pieces of DNA at the end of chromosome 4 (genetic location: 4q35), the so-called D4Z4 deletion. This results in expression of the harmful DUX4 gene and production of a toxic protein (DUX4) that causes dystrophy (fatty replacement) of the skeletal muscles (13). The conversion of DNA into functional products for the cell, such as proteins, is dependent on both the DNA code itself (genetics) as well as on factors that may affect the activity of genes (gene expression), so-called epigenetic factors (14, 15). Epigenetic phenomena determine the "open" or "closed" state of parts of the genome and, thus, control the "on" or "off" position of genes. This can take place by means of changes in methylation, RNA molecules (intermediates between DNA and protein), or by the so-called histone proteins that are involved in the packing (and hence access) of the DNA in the chromosomes. FSHD is, therefore, an epigenetic disease (15). In FSHD patients, the degree of methylation of the DNA influenced by epigenetic factors plays an important role. Sometimes a small molecule group is added to the DNA, a so-called methyl group, which carries additional information. FSHD patients with a D4Z4 deletion (FSHD-1) show a decreased methylation of the D4Z4 region on the chromosomes 4q and 10q (Figure 5).

However, the degree of methylation is not already determined at birth. It varies between persons and may change under the influence of environmental factors during one's lifetime.
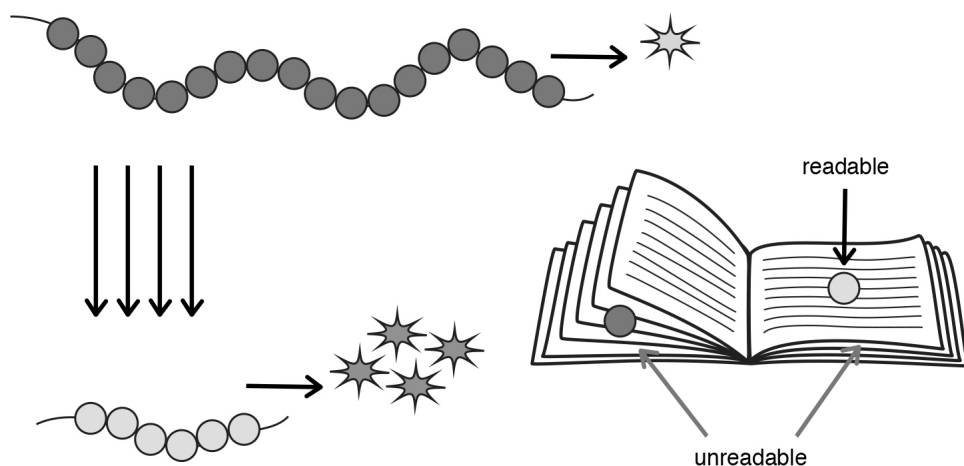
Figure 5 The role of epigenetic factors in facioscapulohumeral dystrophy

If the DUX4 gene is "readable" (i.e. can be transcripted), the DUX4 protein, which is toxic for skeletal muscles, is produced. Epigenetic factors can make it an "unreadable" gene by an increase in methylation. Figure courtesy of Sylvère van der Maarel.

Epigenetic factors ensure that the genetic defect in different people, even within families, can be expressed differently (16). In recent research, the difference in severity of the disease within families with FSHD is, among other phenomena, attributed to epigenetic factors (17).

An increase in physical activity and/or physical exercise can cause changes in the DNA methylation of healthy persons (18). It is possible that a physically active lifestyle is an epigenetic factor for FSHD and can slow down the progression of fatty replacement of muscle tissue by changes in DNA methylation. It is not a coincidence that the perpetuating factors of fatigue, i.e. physical inactivity, sleep disorders and pain, are known epigenetic factors (19). The degree of methylation can be different for every individual cell under the influence of epigenetic factors. This could be an explanation for the differences in effect on the fatty replacement between different muscles of patients with FSHD after CBT and AET, as measured by quantitative magnetic resonance imaging (MRI) (20). To conclude, the first hypothesis is that AET as well as CBT influence the fatty replacement of muscle tissue by modifying epigenetic mechanisms.

Theory of inflammation

A second explanation can perhaps be found in the beneficial effect of physical activity on inflammation. Inflammatory reactions seem to play a role in the increase in fatty replacement of muscle tissue in patients with FSHD and also in the development of chronic experienced fatigue in various neurological disorders (21). In approximately 5% of the muscles of patients with FSHD, edema has been observed using MRI (20, 22). There is evidence that an increase in edema is preceded by inflammation and is followed by fatty replacement of the muscle tissues (23, 24). The inhibition of inflammatory reactions could, therefore, theoretically slow down the progression of the disease. In healthy people, the anti-inflammatory effect of physical activity has already been proven extensively (25). Not only immune cells produce molecules that play a role in inflammatory responses (cytokines). Skeletal contracting muscles also release significant amounts of interleukin IL-6. IL-6 is a pro-inflammatory cytokine, in this situation also called a myokine. IL-6 causes inflammation when it is excreted as a cytokine by immune cells, but fights inflammation when it is released as a myokine by muscle cells. This is most likely because other cytokines are not produced anymore and another, "healthier" environment has been created (26, 27). In healthy adults, the production of IL-6 during exercise is for at least 50% related to the intensity and duration of the exercise (28, 29). To conclude, the second hypothesis is that AET and CBT influence the fatty replacement of muscle tissue by positively influencing inflammatory reactions. This again argues in favor of a physically active lifestyle beyond physical exercise of limited duration.

COMPARISON WITH PREVIOUS RESEARCH

Aerobic exercise in muscle disease: from a discouraging to an encouraging approach

At the time of the design of the FACTS-2-FSHD study, clinicians were reluctant to prescribe exercise to patients with FSHD. They often referred to possible muscle damage due to overuse.

This assumption, however, was based on studies in which mdx mice with muscular dystrophy had to run in a treadmill for days (30). Because mdx mice constitute a model for Duchenne muscular dystrophy only, the results cannot be extrapolated to other neuromuscular disorders, including FSHD. However, evidence from human exercise studies in FSHD was scarce as well. Only one pilot study was conducted with a healthy control group that described the beneficial effect of exercise in

patients with FSHD (31). At the time, there was only limited evidence for a positive effect of exercise in other muscle diseases too. The original Cochrane review from 2005, which described the effect of AET and strength training in muscle disease, contained only two randomized controlled trials (RCTs) and concluded: "In myotonic dystrophy and facioscapulohumeral muscular dystrophy moderate-intensity strength training appears not to do harm, but there is insufficient evidence to establish that it offers benefit. Limitations in the design of studies in other muscle diseases prevent general conclusions in these disorders (32). "The conclusions of the other Cochrane reviews within the neuromuscular disorders group, which described the effect of exercise in amyotrophic lateral sclerosis (ALS), McArdle and peripheral neuropathies, were also limited because of the low number of exercise studies of sufficientquality (33-35).

Throughout the duration of the FACTS-2- FSHD study, the Cochrane review on the effect of AET and strength training in muscle diseases compared with no training has been updated twice (36, 37). The third update is close to completion and is expected to include nine studies including (in addition to the FACTS-2-FSHD study) an RCT with a beneficial effect of AET in FSHD (38) and RCTs with positive effects of AET in Duchenne muscular dystrophy (39), polymyositis and dermatomyositis (40). This expected Cochrane update starts a new era in which exercise is encouraged (rather than discouraged) in patients with FSHD and other muscular disorders.

Aerobic exercise in FSHD

In the FACTS-2-FSHD study, as previously mentioned, no significant effect was observed on aerobic capacity, in contrast to two other studies from Denmark, which investigated the effect of cycling exercises in FSHD: the aforementioned pilot study with a healthy control group (29) and a recently published RCT (38). The absence of an increase in aerobic capacity as observed in the FACTS-2-FSHD study could be explained by a limited adherence to the exercise sessions. Many participants in the FACTS-2-FSHD study did not participate in all the 48 exercise sessions. The participants in the Danish RCT (38) also had a limited adherence. In that study, participants with a reduced adherence (6 of 41) were not included in the analysis, which may explain the positive result. The FACTS-2-FSHD study used an intention-to-treat analysis and had only one dropout, so the risk of bias is smaller when it comes to estimating a realistic effect. Another explanation for the differences between the studies can be found in the prescription of the exercise and the assessment of the outcomes. In the Danish studies, the exercise intensity and the aerobic capacity were determined with a maximum test. However, the

Danish patients were on average younger and less severely affected than the patients in the FACTS-2-FSHD study.

In the FACTS-2-FSHD study, the exercise intensity was determined using the Karvonen method, which uses the resting heart rate and the estimated maximum heart rate (41). The aerobic capacity was measured using a (submaximal) Åstrand cycling test (42). Both methods use an estimate of the maximal oxygen uptake. As the study population in the FACTS-2-FSHD study consisted for a large part of relatively severely affected elderly patients, a maximal test was not considered appropriate. A possible explanation for the lack of increase in aerobic capacity may be that an increase in aerobic capacity is not really possible in this population. Moreover, the exercise prescription based on the Karvonen method might not have been optimal. Finally, the Åstrand method may not be valid for estimating the aerobic capacity in an older, relatively severely affected population of patients with FSHD.

Another notable difference between the studies is that, unlike in the FACTS-2-FSHD study, in the Danish study, in spite of an improvement of aerobic capacity, no effect of AET was observed on physical activity (measured with accelerometry), experienced fatigue (measured with a visual analogue scale (VAS) score) or muscle strength (measured by dynamometry). A VAS-fatigue and dynamometry are less valid and sensitive instruments than the Checklist Individual Strength (CIS) and Quantitative Muscle Assessment, respectively. Again, the question arises whether, in the FACTS-2-FSHD study, adhering to a more physically active lifestyle has caused the observed increase in muscle strength and decrease in experienced fatigue. Until now, an increase in physical activity or muscle strength has not been found in any other exercise trial in FSHD, not even after strength training (31, 38, 43).

EXERCISE IS MEDICINE

What proved to be impossible in drug trials up to now did succeed in research using behavioral interventions. AET as well as CBT did not only reduce the degree of disease burden, but also established a beneficial effect at the muscular level probably as a result of increased physical activity. Table 1 shows the history of interventional research in FSHD. The question arises whether the "number needed to treat" and the (minor) side effect profile based on the FACTS-2-FSHD trial can be achieved with medication in future studies (44).

Table 1: Demographics and baseline characteristics of FSHD patients

Intervention	Effect	NNT
Pilot studies		
Prednison (45, 46)	No	n.a.
Albuterol (47)	No	n.a.
AET (31)	Yes	n.a.
Electrical stimulation and exercise (48)	Yes	n.a.
Randomized controlled trials		
Albuterol (49)	No	n.a.
Albuterol and strength training (50)	No	n.a.
Salbutamol (51)	No	n.a.
AET and CBT (52)	**Yes**	**2.3 and 1.3**
AET (38)	**Yes**	**2.1**

There is no effect of medication on the primary outcome measure in contrast with a positive effect of rehabilitation interventions (in bold letters). AET: aerobic exercise training, CBT: cognitive behavioral therapy; NNT: number needed to treat. The NNT is the number of patients who need to be treated to prevent one additional bad outcome.

Nevertheless, the scientific acceptance of AET and CBT as medicine in FSHD is still difficult. Although both interventions were examined "lege artis" and were based on a theoretical model of perpetuating factors of experienced fatigue, there is still uncertainty (and even scepsis) with regard to the underlying mechanisms. Figure 6 is a nice illustration of the current situation with regard to believers and non-believers.

FOKKE & SUKKE
WETEN WAAR HET IN DE WETENSCHAP OM DRAAIT

ZEER INDRUKWEKKEND, COLLEGA....

MAAR WERKT HET OOK IN THEORIE?

Figure 6 The scientific acceptance of aerobic exercise and cognitive behavioral therapy as medicine is still difficult

In English: Fokke and Sukke know what science is about: "very impressive, colleague, but does it also work in theory?" Source: J. Reid, B. Geleijnse, JM van Tol.

The acceptance of functionally targeted interventions can possibly be accelerated by providing more evidence for underlying mechanisms through basic research. However, the biggest challenge is to get the scientific and clinical world moving forward. This requires a societal change. A change in lifestyle requires a greater effort from patients and practitioners than taking or prescribing a drug. And even medication adherence is limited (45). In CBT, therapy sessions are usually structured by a collaboratively agreed-on agenda. Homework sessions encourage active participation. And during AET, patients exercise at home in addition to supervised training. Research has shown that a patient-centered approach improves treatment adherence in chronic patients and also improves job satisfaction in health professionals (53).

Recently, a new definition of health has been introduced by Huber, in which health is no longer described simply as the absence of disease (54). Policy makers, researchers and clinicians have always had a rather narrow, biomedical interpretation of health, paying particular attention to bodily functions, whereas patients themselves often strived for a broader definition for the concept of health. The new, more positive definition of health is "the ability to adapt and to self-manage, in the face of social, mental and physical challenges of life." This means that a patient with FSHD, despite his or her muscle weakness, can still be healthy if there is a balance in the demands and personal aims of everyday life and if (s)he experiences sufficient self-control and meaning in life. Through an increase in autonomy and active participation, which is the aim of both CBT and (to a lesser extent) AET, the perceived health status can improve further. Although most physicians still tend to adhere to a narrow, biomedical definition of health, rehabilitation medicine has already embraced a more functionally oriented definition of health since its existence. Therefore, Huber's definition of health corresponds well with the focus of rehabilitation medicine to promote autonomy and independence in human beings independent of their disease status.

THE FACTS-2-NMD CONSORTIUM

The FACTS-2-FSHD study was part of a research consortium named FACTS-2-NMD. Within this consortium, a comparable study evaluating AET and CBT was conducted in post-polio syndrome (PPS) and ALS (the FACTS-2-PPS (55) and FACTS-2-ALS study (56), respectively). In addition, the qualitative FACTS-2-PERSPECTIVES study ran parallel to the three intervention trials, making use of a responsive assessment methodology. Within the FACTS-2-FSHD study, patient perspective data from 28 participants and five practitioners were gathered through interviews and focus groups.

In the meantime, the results of the FACTS-2-PPS study have been published (57). This RCT did not demonstrate any change in fatigue, activities or quality of life after AET or CBT, compared with usual care. A possible explanation for the discrepancy with the FACTS-2-FSHD study results may lie in a difference in the level of physical activity between the two populations. Patients with PPS seem to be on average just as active as healthy subjects of the same age (58). They generally are not captured in a negative spiral due to physical inactivity, in contrast to patients with FSHD (59). For patients with PPS, it is not only difficult to bring about an increase in physical activity, but there is also a realistic risk of overload. The results of the FACTS-2-ALS and the FACTS-2-PERSPECTIVES studies are expected soon.

METHODOLOGICAL CONSIDERATIONS

The FACTS-2-FSHD study has some methodological shortcomings. Of these, the limited adherence and the use of the Karvonen method for the determination of exercise intensity have already been mentioned.

Validity and appropriateness of the Åstrand test

Unfortunately, the submaximal Åstrand test proved not to be suitable for the determination of aerobic capacity in patients with FSHD. When performing the Åstrand test, muscle weakness instead of aerobic capacity was a limiting factor in 10% of the participants, so the test results were invalid. Moreover, in 24% of the participants, it was not possible to conduct a valid Åstrand test because of the use of beta-blocker medication. The Åstrand test is, thus, less valid and has also a limited applicability in patients with FSHD. A more reliable test to determine the exercise intensity and/or aerobic capacity in patients with FSHD, particularly in those who are relatively severely affected, is not yet available.

Blinding

Although physiotherapists who performed the physical tests were blinded, blinding of participants was not possible. Especially when using a self-report primary outcome measure (CIS-fatigue), this may have led to bias on the basis of a Hawthorne or placebo effect. The Hawthorne effect is a psychological phenomenon that produces an improvement in human behavior or performance as a result of increased attention from therapists or outcome assessors (60). A placebo effect can be due to specific expectations that patients may have about the efficacy of the treatment they receive (61). This is why the FACTS-2-FSHD trial received only a "Class III" label of evidence by the journal Neurology, whereas the results of the

MRI study received a "Class II" label by the same journal. Hawthorne or placebo effects allow the possibility that the observed effects are not directly related to the specific biological or psychological effects of the treatment. However, as the level of experienced fatigue was still reduced after 12 weeks of CBT and AET compared with the control group and we substantiated our results with MRI parameters, it is very unlikely that the observed effects would be solely due to a placebo or Hawthorne effect.

Randomization

To obtain sufficient power, the participants in the control group had to be randomized again to one of both intervention groups. Fortunately, an analysis revealed that there was no difference at the start of the intervention between the groups with regard to the primary and secondary randomization. Performing a cross-over trial was not a viable alternative, since an adequate wash-out period could not be determined due to the possibility of carry-over effects (even after a substantial wash-out period).

Selection bias

In comparison with other studies, the participants in the FACTS-2-FSHD study indicated a lower pain score as measured with the VAS. On average, the VAS score was 24 on a scale of 0 to 100. In other studies, higher mean VAS scores were found: from 44 (62) to 45 (63). Only a small number of patients in the FACTS-2-FSHD study had a high VAS score. At baseline, 63% of the patients had a VAS score lower than 25 and only 14% had a VAS score greater than 50. This may have been because the participants were a selected group of patients. When patients experience great pain, they are probably less eager to participate in a study that requires an increase in physical activity and that is focused primarily on the treatment of experienced fatigue instead of pain. Moreover, during the qualitative interviews in the FACTS-2-PERSPECTIVES study, participants did not mention pain as an important theme. Interviews with the CBT therapists showed that the module "unhelpful cognitions regarding pain" had been used infrequently (unpublished data). The patient population in the FACTS-2-FSHD study did not differ in demographic characteristics from the 139 patients included in the study by Kalkman et al. (1). From this perspective, the participants included in the FACTS-2-FSHD study seem to constitute a representative sample of the Dutch population of patients with FSHD.

RECOMMENDATIONS

It seems that regular physical activity is at least essential to obtain a decrease in fatigue in patients with FSHD. In those patients, the statement "I'm too fatigued to be physically active" should therefore be changed into: "I'm fatigued, so I need to be physically active." Therefore, both interventions (AET and CBT) should be made available to all patients with FSHD and severe experienced fatigue given the positive results of the FACTS-2-FSHD study.

In addition, one can expect that both interventions are also beneficial to patients with no or relatively minor fatigue for improving and maintaining their functional capacities. The favorable effects of physical activity on the slowing down of fatty muscular infiltration (CBT and AET) and on muscle strength (AET) will probably also occur in patients with much lower levels of fatigue.

AET or CBT?

In the FACTS-2-FSHD study, the effect of AET and CBT was compared with a waiting-list condition consisting of usual care. A logical question is whether one should prescribe primarily CBT, AET or perhaps both interventions to patients with FSHD and severe fatigue? A combination of both could possibly be even more effective, but requires a larger investment of both practitioners and patients with possibly a negative impact on compliance and costs. Both interventions cannot be seen separately from each other. CBT contains a module directed at the optimization of physical activities. And in order to maximize the impact of AET, unhelpful cognitions regarding physical activity have to be discussed and possibly changed. The results of the FACTS-2-FSHD study cannot definitively answer the aforementioned question, nor can they answer the question whether AET is more effective than CBT (or vice versa), because the study was not sufficiently powered for this comparison. Given the small differences in effect size between CBT and ART, such a comparison would require many more participants per group and an international consortium, given the low prevalence of FSHD in the Netherlands. For the time being, both treatments can be implemented in daily practice depending on the local facilities. A combination treatment could be helpful in individual cases, especially when, in addition to an effect on physical activity and fatigue, an effect on muscle strength and/or aerobic capacity is aimed for. The departments of Rehabilitation and Neurology of the Radboud University Nijmegen Medical Center have developed the ENERGETIC program (64). This rehabilitation program combines AET, supervised by a physiotherapist, and energy-conservation

strategies, supervised by an occupational therapist, in a self-management group program to improve social participation, physical endurance and alleviate fatigue. An RCT that evaluates the (cost-) effectiveness of the "ENERGETIC" program has been conducted and the results are awaited soon. In all cases, the recommendation for treatment should match with the individual goals, wishes and needs of the patient and take into account relevant personal and environmental factors.

AET: exercise as medicine

Currently, evidence-based exercise prescriptions do not exist for patients with FSHD. Both patients and clinicians experience difficulties in preparing training programs (65). The recommendations for an effective aerobic exercise program by the American College of Sports Medicine are difficult to adhere to by many patients with FSHD: 20 to 60 minutes AET, 3 to 5 days per week at an intensity of 40 to 85% of the heart-rate reserve (66). The results of the present study will be used to set up an AET standard for patients with neuromuscular disorders for use in rehabilitation centers and physiotherapy practices. The results of the FACTS-2-FSHD study and the experiences of the physiotherapists showed that the Borg scale, the talk test (which means that one can carry on a light conversation while exercising), and the rule that activities of daily life should not be negatively influenced by the exercise program are useful indicators for a proper exercise intensity (67). Previous research from Canada has shown that, in clinical practice, the exercise intensity is frequently determined based on simple tests such as the response of participants to the training, the Borg scale and/or the talk test (68).

In any case, to maintain the highest possible compliance, it is recommended to prescribe exercise as medicine with a clear description of exercise duration, frequency, intensity, location and supervision, and to search for a physical activity that the patient prefers. The barriers that patients still experience when exercising such as costs, shame for their limitations, and lack of facilities should be taken into account (69). It is for a reason that the FSHD lifestyle guide (70) refers to "one has to move, if possible. " It is important to realize that a patient does not always have to exercise. The results of the FACTS-2-FSHD study emphasize the relevance of a physically active lifestyle. Ideally, an intervention for the improvement of chronic fatigue would no longer be needed. When adherence to a physically active lifestyle is already recommended shortly after the diagnosis, and physical activity and exercises are maintained, a patient may not be caught in a downward spiral as a result of physical inactivity.

CBT: part of rehabilitation

The beneficial effect of CBT was not only larger than expected, but also applicable to more domains than expected. In the future, CBT should be implemented as part of rehabilitation treatment for patients with FSHD and chronic fatigue. The message that AET has a positive effect in FSHD has been expressed increasingly in recent communications related to research and healthcare. However, in spite of the positive and long-lasting effects of CBT as observed in the FACTS-2-FSHD study, it will take more time before CBT will receive the same amount of attention. The scientific evidence for the effect of AET in neuromuscular disorders is growing steadily. Yet, until now, a positive effect of CBT in neuromuscular disorders has been described only in the FACTS-2-FSHD study. Nevertheless, it is expected that the promotion of CBT as an intervention for neuromuscular disorders can develop equally to AET. Currently, an international study on the effect of CBT with and without AET in patients with myotonic dystrophy type 1 is being conducted, the OPTIMISTIC study (71).

Not every rehabilitation center or hospital will have a sufficient number of psychologists qualified in CBT.

Implementing CBT as standard care in rehabilitation can therefore be difficult, also because of the costs of a psychological treatment. To solve this problem, the principle of "stepped care" could be applied. Stepped care means that the most effective yet least resource-intensive treatment is delivered to patients first, only "stepping up" to more intensive treatments when clinically required. Step one can be the implementation of CBT techniques such as increasing physical activity through a graded activity program by physical and/or occupational therapists, and help to adhere to regular sleep–wake times and change unhelpful thoughts by rehabilitation physicians (72). To further optimize the effect of CBT and in the case of psychopathological symptoms, counseling by a psychologist specialized in CBT can be administered as a second step. CBT has to be considered as medicine too. The psychologist will have to prescribe which specific modules have to be followed. Almost always, the dysregulation of physical activity module will be part of the treatment. CBT can also be supported by e-health, for example by using an interactive application, in order to save costs (73).

GENERALIZABILITY

During the FACTS-2-FSHD study, both interventions were performed at several locations by multiple therapists according to the same protocol. This multi-centeredness implies that the treatment protocols should be implementable in other rehabilitation practices in the near future.

From the results of the FACTS-2-FSHD study, it cannot be concluded that AET and CBT will also be effective to reduce fatigue in patients with other neuromuscular disorders than FSHD. If epigenetics, inflammation and the downward spiral as a result of physical inactivity are important explanatory mechanisms of effect in FSHD, it is not justified to extrapolate the results to other neuromuscular disorders. The negative results of the FACTS-2-PPS trial confirm this notion. Moreover, it is unknown whether the results can be generalized to patients with FSHD without severe fatigue. Of course, in daily rehabilitation practice, reducing cardiovascular risk factors is often a secondary objective of exercise therapy. Previous studies have shown that patients with neuromuscular disorders, including FSHD, are at a greater risk of developing metabolic syndrome (74, 75). Thus, a physically active lifestyle, taking into account the preventive effect on chronic disease and the beneficial effects on fatty replacement in muscles (CBT and AET) and muscle strength (AET), can be recommended also to FSHD patients without severe fatigue with the aim to improve and maintain their functional capacities and health.

FUTURE PERSPECTIVES

To better interpret and implement the results of the FACTS-2-FSHD study, further research is necessary. This research will have to focus both on the underlying mechanisms of the observed effects and on improving the methodological shortcomings as previously described.

Molecular signature

In order to better explain the positive effects on the fatty replacement of muscles, the molecular signature of both interventions (CBT and AET) has yet to be found. The aforementioned assumptions regarding the role of epigenetic factors and inflammation could be confirmed or refuted by conducting a study with AET and/or CBT including DNA analysis of muscle tissue and analysis of blood samples for the determination of myokines and cytokines before and after the intervention. The previously mentioned "OPTIMISTIC" trial already uses an unbiased approach to determine the molecular signature of both CBT and AET. This is unusual. Usually, an intervention starts with basic research, while in a later stage its impact on daily functioning and social participation are measured. Here, basic research may explain in a later phase the observed effects of AET and CBT on the functioning and participation of patients with FSHD ('reverse translational research'). The long-term effect on fatty replacement of muscle tissue should be observed in a longitudinal study. However, such a study will be labor- and cost-intensive because of repeated MRI measurements.

Optimizing life balance

Within the CBT module directed at dysregulation of physical activity, regaining a balance in physical activities throughout the day and week is a key goal. However, the concept of activity encompasses more than just physical activity. "Life balance" refers to a highly personalized construct that includes balancing both the physical demands and the more complex role demands (e.g. as employee, parent, or volunteer), while preserving and creating meaning in life. Patients with FSHD often experience their lives as "out of balance" due to the perceived burden of disease as shown in Figure 4. It is a big challenge for them to balance all their current and future activities with their physical and mental capacities. Too many and too heavy activities can lead to overload, but having too few meaningful activities also leads to an unsatisfactory situation. Of course, the degree of fatigue is an important factor herein. The life balance of the patient in the reported case study was better after CBT. He was able again to combine social activities with work. Within the field of rehabilitation medicine, there is a growing interest in self-management programs that are based on the use of energy-saving strategies (64). It is expected that an optimal life balance is also of importance for the degree of social participation. However, the concept 'life balance' is very difficult to measure because it concerns the duration and intensity of selected activities as well as the personal meaning of these activities. Until now, mainly measurement instruments at the ICF level of impairments are available for patients with FSHD. Future research should, therefore, focus on validating outcome measures at the ICF levels of activities and participation with a focus on the construct of 'life balance.' Currently, a new outcome measure is being validated to measure the degree of disease burden in patients with FSHD: the FSHD Health Index (HI FSH) (76).

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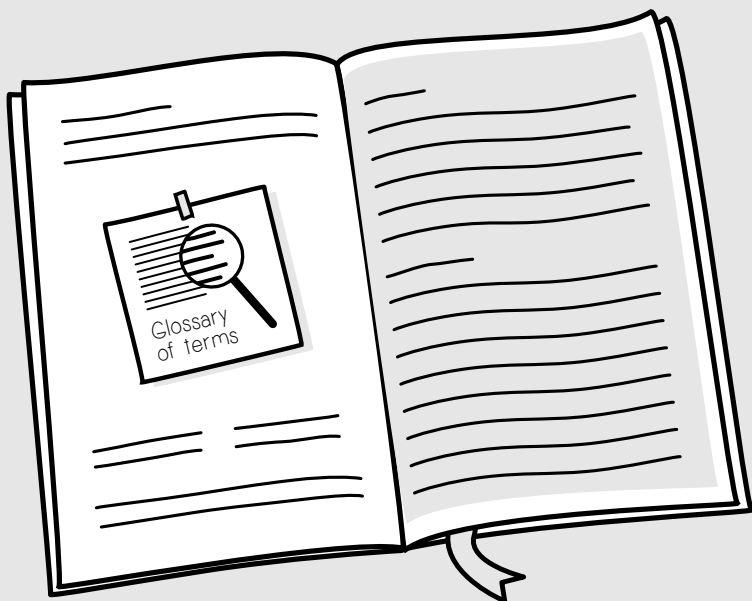
GLOSSARY OF TERMS

^{1}H	proton
1RM	one repetition maximum
^{31}P	phosphorous
6MWT	six-minute walk test
ACSM	American college of sports medicine
AET	aerobic exercise training
AFQ	abbreviated fatigue questionnaire
AL	adductor longus
ALS	amyotrophic lateral sclerosis
AM	adductor magnus
AP	action potential
ARR	absolute risk reduction
BDI	Beck depression index
BDI-pc	Beck depression inventory primary care
BF%	body fat percentage
BFL	biceps femoris long head
BFS	biceps femoris short head
BMD	Becker muscular dystrophy
BMI	body mass index
CAF	central activation failure
CBT	cognitive behavioral therapy
CCMO	centrale commissie mensgebonden onderzoek
CI	confidence interval
CIS	checklist individual strength
CIS-activity	physical activity subscale of the checklist individual strength
CIS-fatigue	fatigue subscale of the checklist individual strength
CK	creatine phosphokinase
CMT	Charcot Marie Tooth
CPEO	chronic progressive external ophtalmoplegia
CRAMP	computer registry of all myopathies and polyneuropathies
CSS	clinical severity score
CT	computer tomography
DM1	myotonic dystrophy type 1
DM2	myotonic dystrophy type 2
DMD	Duchenne muscular dystrophy
DMPK gene	dystrophia myotonica protein kinase gene
DN4	douleur neuropathic 4
EDL	extensor digitorum longus
ENMC	European neuromuscular centre

ESS	Epworth sleepiness scale
FACTS-2-FSHD	acronym for Fitness And Cognitive behavioral TherapieS / for Fatigue and ACTivitieS in facioscapulohumeral dystrophy
FACTS-2-NMD	acronym for Fitness And Cognitive behavioral TherapieS / for Fatigue and ACTivitieS in neuromuscular disorders
FFM	fat-free mass
FFMI	fat free mass index
FOV	field of view
FSHD	facioscapulohumeral dystrophy
FSS	fatigue severity scale
FTI	force time integral
G	gracilis
HADS	hospital anxiety and depression scale
HI FSH	FSHD health index
HRR	heart rate reserve
ICC	intraclass correlation coefficient
ICF	international classification of functioning, disability and health
IT	inversion time
LGMD	limb girdle muscular dystrophy
MDiff	mean differences
MET	metabolic equivalent
MIRS	muscular impairment scale
MRI	magnetic resonance imaging
MRS	magnetic resonance spectroscopy
MVC	maximal voluntary muscle force
MVIC	Maximum voluntary isometric strength
NHP	Nottingham health profile
NHP-sleep	sleep subscale of the Nottingham health profile
NMD	neuromuscular disorders
NMR	magnetic resonance spectroscopy
NNGB	Dutch standard for healthy exercise
NNT	number needed to treat
NP/NA	non-participant/ not available for MRI study
NPSI	neuropathic pain symptom inventory
NRS	numeric rating scale
PCr	phosphocreatine
Pi	inorganic phosphate
PPS	post-polio syndrome
PROMM	proximal myotonic myopathy

PSQI	Pittsburgh sleep quality index
qT2-MRI	quantitative T2-MRI
RCT	randomized controlled trial
REE	resting energy expenditure
REVMan	review manager 5
RF	rectus femoris
RM	repetition maximum
ROI	region of interest
S	sartorius
SCL-90	symptom checklist-90
SF-36	short form 36
SFQ	short fatigue questionnaire
SIP	sickness impact profile
SIP68-sb	social behavior subscale of the Sickness Impact Profile 68
SM	semimembranosus
SMA	spinal muscular atrophy
SNR	signal to noise ratio
ST	semitendinosus
TE	echo time
TEE	total daily energy expenditure
TIRM	turbo inversion recovery magnitude
UC	usual care
UNS	Unnalinna narcolepsy scale
VAS	visual analogue scale
VI	vastus intermedius
VL	vastus lateralis
VM	vastus medialis
VO2max	maximal oxygen uptake
VSN	vereniging spierziekten Nederland
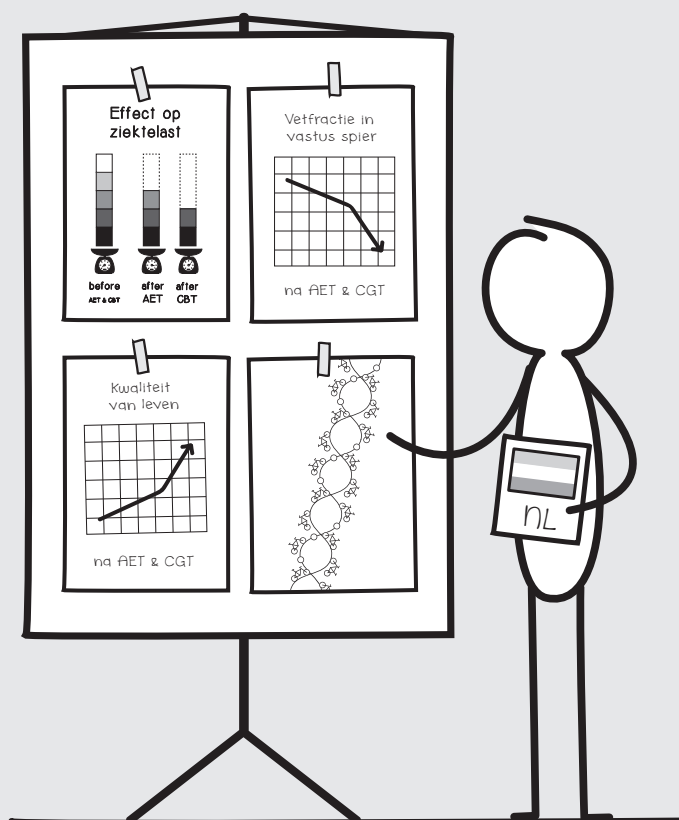
SAMENVATTING

SAMENVATTING

Facioscapulohumerale musculaire dystrofie (FSHD) is de op twee na meest voorkomende spierdystrofie met een geschatte prevalentie van 1 op de 8.000 personen wereldwijd. Het is een erfelijke aandoening met autosomaal dominante overerving, waarbij allereerst de gezichtsspieren en spieren van de schoudergordel progressief verzwakken en later meestal ook de rompspieren en arm- en beenspieren. In het afgelopen decennium is al veel inzicht verworven in de onderliggende moleculair genetische oorzaak. De oorzaak van FSHD is in meer dan 95% van de gevallen te vinden in het ontbreken van bepaalde stukjes DNA (D4Z4) op chromosoom 4q35. Hierdoor komt er een giftig eiwit, DUX4, in de spiercellen vrij. Het is echter nog niet bekend waarom de mate, de verdeling en de progressie van spierzwakte van patiënt tot patiënt zo verschillen. Bovendien zijn er geen biomarkers beschikbaar om de ernst en progressie van FSHD objectief te kunnen beoordelen.

Tot op heden is er geen curatieve behandeling beschikbaar voor patiënten met FSHD. Hoewel de levensverwachting niet duidelijk beperkt is, wordt uiteindelijk 20% van de patiënten rolstoelafhankelijk door de spierzwakte. Bovendien ervaart meer dan 60% van de patiënten ernstige en chronische vermoeidheid, wat de mate van sociale participatie vermindert en de ziektelast vergroot. Fysieke inactiviteit bleek uit eerder onderzoek de belangrijkste in stand houdende factor van deze ervaren vermoeidheid bij patiënten met FSHD. Fysiek actief zijn én blijven is echter door de spierzwakte moeilijk voor patiënten. Dit kan vervolgens leiden tot een vicieuze cirkel van vermoeidheid, inactiviteit en afname van sociale participatie.

De twee belangrijkste doelstellingen van dit proefschrift waren:

- De beschrijving van vermoeidheid en inactiviteit bij neuromusculaire aandoeningen (deel 1).
- Het bestuderen van het effect van twee, op een theoretisch model gebaseerde, behandelingen die beogen de mate van activiteit te optimaliseren en de ervaren vermoeidheid te verminderen bij patiënten met FSHD (deel 2).

Hoofdstuk 1 is de algemene inleiding van het proefschrift en verstrekt achtergrondinformatie over FSHD. Het klinische beloop van FSHD is tussen personen sterk variabel. Deze variabiliteit doet vermoeden dat epigenetische mechanismen een rol spelen. Epigenetica wordt gedefinieerd als de erfelijke veranderingen in genactiviteit en genexpressie die plaatsvinden, ook gedurende het leven, onafhankelijk van veranderingen in de DNA volgorde.

Vermoeidheid wordt in toenemende mate herkend én erkend als een belangrijk klinisch probleem bij veel aandoeningen. Voor verscheidene patiëntpopulaties worden nu ook evidence-based behandelprogramma's ontwikkeld. Ook meer dan 60% van de patiënten met FSHD, gemeten met de subschaal vermoeidheid van de Checklist Individuele Spankracht (CIS-vermoeidheid), een multidimensionale vermoeidheidsvragenlijst, bleek ernstige vermoeidheid te ervaren. Fysieke inactiviteit, slaapstoornissen en pijn bleken in volgorde van belangrijkheid bij te dragen aan het in stand houden van vermoeidheid bij patiënten met FSHD. Spierzwakte draagt bij aan fysieke inactiviteit, en daarmee indirect aan (toename van) vermoeidheid. Dit model van in stand houdende factoren van vermoeidheid vormde de basis voor het in dit proefschrift beschreven en gebruikte behandelprotocol van de FACTS-2-FSHD studie (acroniem voor Fitness And Cognitive behavioral TherapieS for Fatigue and ACTivitieS in FSHD). Dit betrof de eerste, op een theoretisch model gebaseerde, klinische trial naar het effect van aerobe training (AT) en cognitieve gedragstherapie (CGT) op ervaren vermoeidheid bij patiënten met FSHD.

Er werd verondersteld dat, om ervaren vermoeidheid te verminderen, twee verschillende behandelingen toegepast zouden kunnen worden: AT om de mate van fysieke activiteit te vergroten en CGT om een actieve levensstijl te stimuleren (maar tegelijkertijd overmatige fysieke belasting te voorkómen). Het primaire doel van deze studie was dan ook om het effect van beide behandelingen op ervaren vermoeidheid bij patiënten met FSHD te evalueren op basis van de CIS-vermoeidheid. Een secundair doel was het effect van beide behandelingen op de bekende in stand houdende factoren van vermoeidheid bij FSHD te evalueren.

De secundaire uitkomstmaten besloegen alle domeinen van de International Classification of Functioning, Disability and Health (ICF). Tevens werd beoogd om klinisch relevante biomarkers te vinden om de progressie van de aandoening en de respons op de behandeling bij patiënten met FSHD te meten met behulp van MRI (Magnetic Resonance Imaging). MRI is namelijk in staat om op relatief eenvoudige wijze intramusculaire fibrose en vervetting van de spieren te visualiseren. Er werd verondersteld dat het daarom een geschikte en objectieve biomarker zou kunnen zijn om de betrokkenheid van individuele spieren vast te leggen en hiermee objectief de ernst en progressie van de spieraantasting bij FSHD te meten.

DEEL 1: VERMOEIDHEID BIJ NEUROMUSCULAIRE AANDOENINGEN

In deel 1 wordt een overzicht gegeven van de prevalentie (het vóórkomen), de meetinstrumenten en de behandeling van vermoeidheid bij neuromusculaire aandoeningen (NMA).

De volgende onderzoeksvragen worden gesteld:

1. Wat is de prevalentie en de relevantie van vermoeidheid bij patiënten met een spierdystrofie?

🚲 Uit **hoofdstuk 2** blijkt dat vermoeidheid een veel voorkomend en ook relevant symptoom is bij patiënten met een spierdystrofie. Het onderscheid tussen ervaren vermoeidheid en spierzwakte, het kenmerkende symptoom van spierdystrofie, kan lastig zijn. Hoewel ervaren vermoeidheid moeilijk te definiëren is, kan het met vragenlijsten wel betrouwbaar gemeten worden, zoals met de CIS-vermoeidheid. Omdat vermoeidheid bij spierdystrofieën een multidimensioneel concept is, is het belangrijk om inzicht te hebben in de onderliggende factoren die bijdragen aan deze vermoeidheid. Volgend op een dergelijke analyse kunnen namelijk preventieve en therapeutische behandelingen worden ontwikkeld. Daarom wordt een overzicht gegeven van de onderliggende pathofysiologie van vermoeidheid bij verscheidene spierdystrofieën en wordt het model van in stand houdende factoren van ervaren vermoeidheid bij FSHD toegelicht. Tot slot wordt een systematisch overzicht van de mogelijke behandelopties van vermoeidheid bij patiënten met spierdystrofie gepresenteerd bestaande uit fysieke training, medicatie en cognitieve gedragstherapie.

2. Hoe kan vermoeidheid bij patiënten met neuromusculaire aandoeningen gemeten worden?

🚲 **Hoofdstuk 3** beschrijft de resultaten van een workshop van het European Neuromuscular Center (ENMC) over pijn en vermoeidheid bij patiënten met NMA. Deze workshop had als doel overeenstemming te bereiken over de definitie voor pijn en vermoeidheid bij NMA en om een eenduidige set van meetinstrumenten voor pijn en vermoeidheid vast te leggen voor deze groep aandoeningen. Zowel pijn als vermoeidheid komen veel voor bij NMA en zijn van grote invloed op veel activiteiten van het dagelijkse leven. Er kan onderscheid gemaakt worden tussen verschillende typen pijn en vermoeidheid,

gerelateerd aan de onderliggende (stadia van) NMA. Dit moet los gezien worden van aspecifieke pijn en vermoeidheid die niet primair gerelateerd zijn aan de onderliggende aandoening. Een verscheidenheid aan methoden wordt gebruikt om pijn en vermoeidheid bij NMA te meten. Om effectieve behandelingen voor NMA te kunnen ontwikkelen moet echter internationaal overeenstemming bereikt worden over de definitie van en de meetinstrumenten voor zowel pijn als vermoeidheid. Daarom wordt tot slot een eenduidige set van meetinstrumenten voor gebruik in toekomstig onderzoek en in de klinische praktijk beschreven.

3. Wat is het effect van training bij spierziekten?

🚲 **Hoofdstuk 4** bestaat uit een Cochrane review waarin de veiligheid en het effect van krachttraining en aerobe training bij mensen met een spierziekte wordt beschreven. Krachttraining en aerobe training zouden spierfunctie en cardiovasculaire functie kunnen optimaliseren en verdere spieratrofie door inactiviteit en conditieverlies kunnen voorkómen bij mensen met een spierziekte. Er werd in de bekende databases gezocht naar gerandomiseerde of quasigerandomiseerde gecontroleerde onderzoeken die krachttraining en/of aerobe training vergelijken met gebruikelijke zorg. De behandeling moest minimaal 6 weken duren en de spierziekte moest op de juiste wijze vastgesteld zijn bij de deelnemers. Vijf onderzoeken voldeden aan deze criteria, met in totaal 170 deelnemers. Er waren twee onderzoeken naar het effect van krachttraining bij FSHD en myotone dystrofie (totaal 101 deelnemers). Twee onderzoeken beschreven het effect van krachttraining in combinatie met aerobe training bij personen met mitochondriële myopathie (18 deelnemers) en myotone dystrofie type I (35 deelnemers). Het laatste onderzoek betrof een onderzoek naar het effect van aerobe training bij personen met polymyositis en dermatomyositis (14 deelnemers). Deze onderzoeken toonden aan dat krachttraining met een matige intensiteit bij mensen met myotone dystrofie of FSHD, en aerobe training bij mensen met dermatomyositis of polymyositis niet schadelijk is voor de spieren. Krachttraining in combinatie met aerobe training bleek veilig te zijn bij myotone dystrofie type I en zou effectief kunnen zijn in het verbeteren van de lichamelijke conditie bij mensen met een mitochondriële myopathie. Tot slot bleek krachttraining niet schadelijk te zijn bij personen met FSHD, myotone dystrofie, mitochondriële myopathie, of dermatomyositis/polymyositis, maar er was onvoldoende bewijs om een positief effect aan te tonen. Door beperkingen in de opzet van de studies konden meer algemene conclusies niet getrokken worden.

DEEL 2: DE FACTS-2-FSHD STUDIE

In deel 2 worden de resultaten van de FACTS-2-FSHD studie beschreven. De volgende onderzoeksvragen worden gesteld:

4. Wat is het effect van aerobe training en cognitieve gedragstherapie op ervaren vermoeidheid bij patiënten met FSHD?

In **hoofdstuk 5** wordt het protocol van de FACTS-2-FSHD studie beschreven. De FACTS-2-FSHD studie is het eerste, op een theoretisch model gebaseerde, gerandomiseerde klinische onderzoek dat het effect en behoud van effect van aerobe training (AT) en cognitieve gedragstherapie (CGT) beschrijft op het verminderen van ervaren vermoeidheid bij patiënten met FSHD. De behandelingen zijn gebaseerd op een theoretisch model van in stand houdende factoren van vermoeidheid bij patiënten met FSHD. Het primaire doel van de FACTS-2-FSHD studie was om het effect van AT en CGT te bestuderen op het verminderen van ervaren vermoeidheid bij patiënten met FSHD type 1 in vergelijking met de gebruikelijke zorg. De verwachting was dat zowel AT als CGT effectief zouden zijn in vergelijking met de gebruikelijke zorg. De gebruikelijke zorg bestaat meestal uit geen enkele behandeling of soms reguliere fysiotherapie. Er werd verwacht dat een eventuele verbetering door AT verkregen zou worden door het verbeteren van de fysieke (aerobe) capaciteit, terwijl de effecten door CGT veroorzaakt zouden worden door veranderingen in de activiteiten van het dagelijks leven en in gedrag. Secundaire doelen bestonden uit het evalueren van het effect van AT en CGT op de bekende in stand houdende factoren van vermoeidheid bij FSHD.
De AT bestond uit fietstraining op een fietsergometer. Dit programma duurde 16 weken en bevatte wekelijks één training onder supervisie van een fysiotherapeut in een revalidatiecentrum en twee keer per week één training thuis. CGT was gericht op alle bekende in stand houdende factoren van vermoeidheid bij FSHD en werd aangepast aan de behoeften van de individuele deelnemer. Elke sessie duurde een uur en werd begeleid door een geregistreerde cognitieve gedragstherapeut. Na de eerste meting werden de patiënten door middel van loting toegewezen aan de AT groep, CGT groep, of een groep die gebruikelijke zorg kreeg. Na een behandelperiode van 16 weken en een follow-up van 3 maanden werd de groep met gebruikelijke zorg opnieuw door middel van loting toegewezen aan ofwel AT ofwel CGT (28 weken na inclusie). De bedoeling was om uiteindelijk 25 volwassen patiënten in elk van de drie groepen in te sluiten: AT, CGT, of gebruikelijke

zorg. Omdat patiënten in de controlegroep alsnog AT of CGT kregen, was het minimum benodigde aantal patiënten 50. Uitkomstmaten werden verkregen bij start van het onderzoek, onmiddellijk na beëindiging van de behandelingen (en controleperiode) en na respectievelijk 12 en 24 weken van follow-up. Een 'linear mixed model for repeated measurements' werd gebruikt om de verschillen tussen de groepen te analyseren.

In **hoofdstuk 6** worden de resultaten van de FACTS-2-FSHD onderzoek beschreven waarvan het protocol in hoofdstuk 5 is toegelicht. In totaal 57 ambulante patiënten met FSHD type 1 en ernstige ervaren vermoeidheid werden door middel van loting toegewezen aan AT, CGT, of gebruikelijke zorg. Na de behandeling was de ervaren vermoeidheid voor zowel de deelnemers in de AT groep (28 deelnemers) als de CGT groep (25 deelnemers) significant afgenomen in vergelijking met de groep deelnemers die gebruikelijke zorg kregen. Dit verschil, gemeten met de CIS-vermoeidheid, was -9,1 voor AT (95% BI: -12,4 tot -5,8) en -13,3 voor CGT (95% BI -16,5 tot -10,2). Dit positieve effect bleef voor beide groepen ook na de follow-up periode bestaan, met een verschil van -8,2 voor AT (95% CI -12,4 tot -5,8) en -10,2 voor CGT (95% BI -14,0 tot -6,3). Na de behandeling was er bij 19 deelnemers in de CGT groep (75%) en 14 deelnemers in de AT groep (50%) geen sprake meer van ernstige vermoeidheid. De 'number needed tot treat' (NNT), het aantal patiënten dat behandeld moet worden om één patiënt te genezen van ernstige vermoeidheid, kwam voor AT daarmee op 2.3 (95% BI 1,4 tot 3,1) met een absoluut risico reductie (ARR) van 50% (95% BI 32 tot 69%). De NNT voor CGT was 1,3 (95% BI 1,1 tot 1,7) met een ARR van 76% (95% BI 59 tot 93%). Bij de CGT groep werden alle in stand houdende factoren van vermoeidheid positief beïnvloed, met uitzondering van pijn. Ook nam de mate van sociale participatie toe. De deelnemers aan de AT groep vertoonden een toename van objectief gemeten fysieke activiteit en maximaal isometrische kracht van de quadriceps. De toename van objectief gemeten fysieke activiteit bij beide groepen en de verbetering van de mate van sociale participatie bij CGT was ook bij de follow-up meting nog steeds aanwezig. Meer dan 70% van de deelnemers in de AT groep en bijna 80% van de deelnemers in de CGT groep bleef fysiek actief, ook na beëindiging van het onderzoek. Bij beide groepen werd geen verbetering in aerobe capaciteit gevonden. Alleen milde bijwerkingen werden gerapporteerd in de AT groep. Het mediaan aantal behandelsessies was veel lager in de CGT groep, namelijk 5, dan in de AT groep (40 sessies). Er werd geconcludeerd dat zowel AT als CGT in staat zijn ervaren vermoeidheid te genezen bij patiënten met FSHD.

5. Zijn er structurele afwijkingen aantoonbaar in skeletspieren van patiënten met FSHD die kunnen dienen als biomarkers voor het meten van ziekteprogressie en behandeleffect?

Ondanks dat het meest relevante onderliggende genetische mechanisme van de aandoening FSHD ontdekt is, is het exacte mechanisme nog niet bekend. Dit is wel noodzakelijk om het proces dat leidt tot vervetting van de skeletspieren beter te begrijpen.

Uit de studie beschreven in **hoofdstuk 7** blijkt dat vetfractie, gemeten door middel van kwantitatieve MRI (q-MRI), zowel een objectieve als een gevoelige biomarker is om betrokkenheid van de spier, zelfs subklinisch, aan te tonen. Uit een analyse van de gemiddelde vetfractie van alle gemeten individuele spieren bleek dat er een zandloperpatroon bestaat van veel spieren: spieren zijn ofwel geheel, ofwel vrijwel niet vervet; weinig spieren zijn gemiddeld vervet. Deze quasibinaire verdeling is niet eerder beschreven voor andere spierdystrofieën, en zou specifiek kunnen zijn voor FSHD. De intramusculaire vetfractie nam lineair toe van proximaal naar distaal. Vervetting van een gehele spier zou, gemiddeld gezien, ongeveer 3,5 jaar duren. De meest steile gradiënt van vervetting werd gezien in de gemiddeld aangedane spieren, wat een aanwijzing kan zijn voor het feit dat deze spieren in relatief korte tijd snel vervetten totdat ze volledig aangedaan zijn. Deze bevinding zou relevant kunnen zijn voor het stellen van de prognose en het bepalen van behandeleffecten bij FSHD.

Het belangrijkste doel van de studie die beschreven wordt in **hoofdstuk 8** is het bepalen van het effect van AT en CGT op de toename van vervetting en het voorkómen van oedeem in individuele beenspieren van patiënten met FSHD type 1 door middel van T2-MRI. Kwantitatieve T2-MRI (qT2-MRI) en vetsuppressie T2-MRI afbeeldingen van het bovenbeen werden verkregen bij start en follow-up van 31 patiënten. Al deze patiënten waren geïncludeerd in de FACTS-2-FSHD studie; 13 van hen kregen de gebruikelijke zorg, 9 AT en 9 CGT. In de groep met gebruikelijke zorg nam de vervetting in de aangedane spieren gemiddeld met 6,7% per jaar toe. Toename van vervetting trad gemiddeld gezien in alle spieren op behalve in de gastrocnemius, sartorius en vastus lateralis. The adductor magnus spier vertoonde de grootste toename van vervetting. Deze toename was significant lager na beide behandelingen. Er was nog maar een toename van 2,9% van vervetting per jaar in de AT groep (95% BI 0,7 tot 5,2; p< 0,05) en 1,7% per jaar in de CGT groep (95% BI -0,2 tot 3,6; p < 0,01). In beide behandelgroepen ontwikkelden een kleiner aantal spieren oedeem in vergelijking met de groep die gebruikelijke zorg kreeg. De

vetfractie in de spieren van alle patiënten bij de eerste meting (gemiddelde waarde voor alle bovenbeenspieren per patiënt) was negatief gecorreleerd met de mate van fysieke activiteit bij de eerste meting (R^2= 0,27; p = 0,0013), gemeten met behulp van de actometer, en met de maximale loopafstand (R^2= 0,40; p < 0,0001), maar niet significant gecorreleerd met aerobe capaciteit. Er werd geconcludeerd dat qT2-MRI een reproduceerbare en gevoelige biomarker is om het effect te meten van een toename van fysieke activiteit in individuele spieren van patiënten met FSHD en dat zowel AT als CGT de toename van vervetting van spierweefsel bij FSHD afremmen.
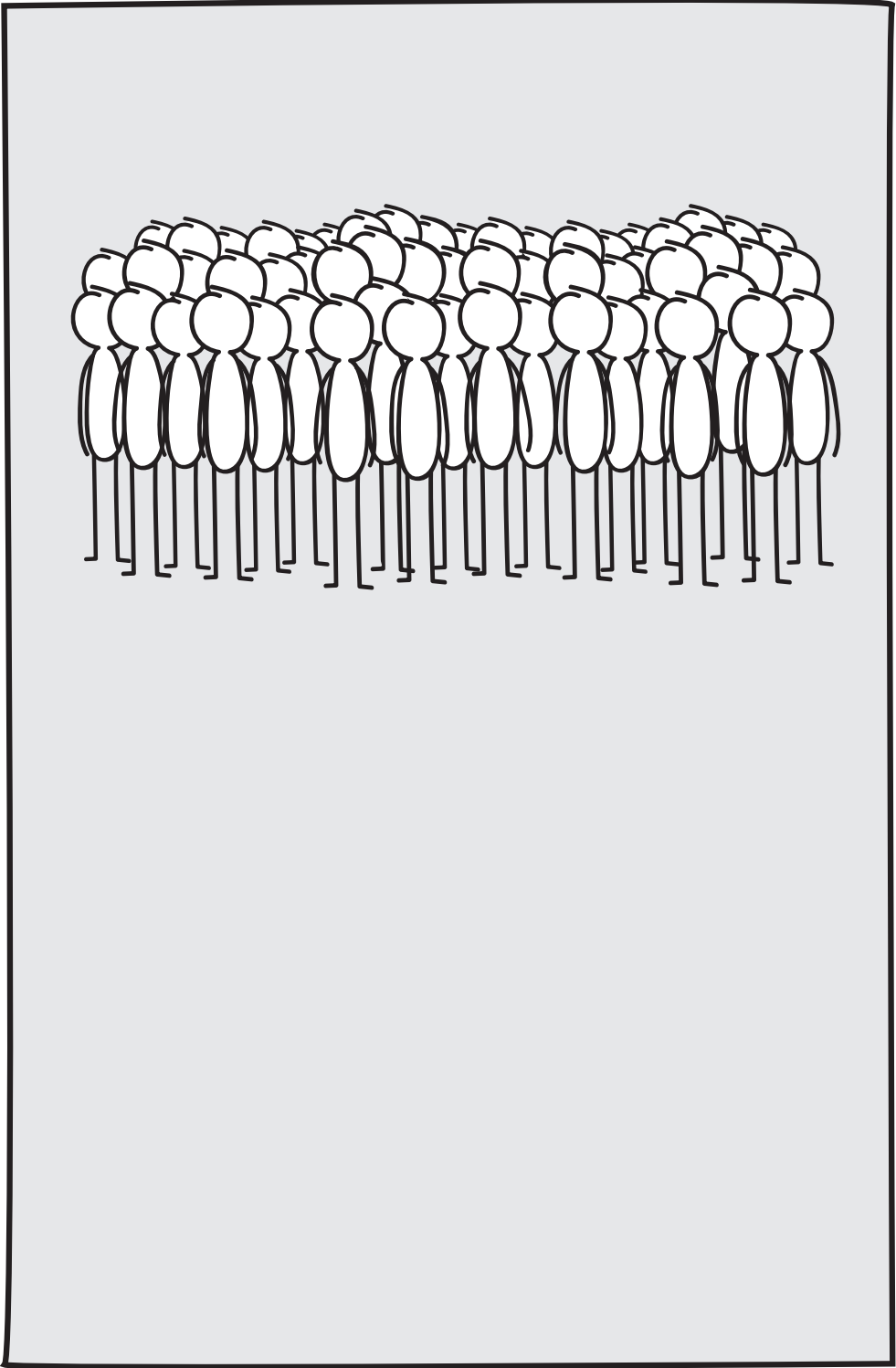
DANKWOORD

Bij het schrijven van het dankwoord besef ik ineens hoeveel mensen bij het onderzoek betrokken zijn geweest. Het zou een tweede deel van het proefschrift vergen om iedereen persoonlijk te bedanken. Het onderzoek was uniek door de samenwerking op alle vlakken, wat mij ook heeft gevormd als wetenschapper, arts én persoon. Dank allen hiervoor!

Allereerst wil ik **alle 57 deelnemers aan het onderzoek** hartelijk bedanken, zonder u was dit proefschrift niet mogelijk geweest. Ik heb u allen als een zeer betrokken groep ervaren. De studie vroeg veel inzet én inspanning die als vanzelfsprekend werd geleverd. De sleutel tot het succes van dit proefschrift lag bij uw inspanning. Door het thuis afleveren van de hometrainers samen met mijn vriend heb ik bij een aantal van u letterlijk en figuurlijk een kijkje in huis mogen nemen. De ervaren gastvrijheid was uniek. Dit heeft mij extra bagage als revalidatiearts en persoon meegegeven en ik heb er heel wat adressen voor een kopje koffie bij gekregen.

Prof. Geurts, beste Sander, ik had mij geen betere eerste promotor kunnen wensen. Je hebt mij de kans gegeven zelfstandig te groeien in mijn carrière als wetenschappelijk onderzoeker, maar ook in de academische wereld. Je reactie op mijn stukken was altijd snel en adequaat. Ik bewonder je kennis en analytisch vermogen. Ik zal niet snel vergeten dat je, om de snelheid van indienen van het manuscript bij Neurology te bevorderen, je commentaar op jouw initiatief telefonisch met mij besprak, vijf minuten voordat je met de camper op vakantie ging.

Prof. van Engelen, beste Baziel, elk gesprek begon allereerst met een persoonlijke vraag, hoe gaat het met de mens achter de onderzoeker? Door als filosoof boven de stof te staan heb je mij unieke inzichten gegeven en gestimuleerd het geheel te overzien. Ik heb vaak driftig meegeschreven om je unieke oneliners te notuleren. Je bent een mensenmens en een netwerker waar ik mij graag aan spiegel. De vele mails en telefoontjes met de boodschap 'ik wil je aan (...) voorstellen' hebben mij een uniek (inter)nationaal netwerk van betrokken onderzoekers bezorgd, een van de meest plezierige arbeidsvoorwaarden van een promotietraject.

Prof. Bleijenberg, beste Gijs, dank voor je hulp bij de opzet, uitvoering en verwerking van de resultaten van het onderzoek, wat ook nog doorging na je emiraat. Met cognitieve gedragstherapie hebben we een unieke vorm van behandeling in handen die de kwaliteit van leven van veel patiënten fors zal verbeteren. Je enthousiasme hiervoor neem ik graag mee in verder onderzoek en de implementatie hiervan. Ook in mijn klinisch werk bij mensen met hersenletsel ervaar ik nu de grote verbeteringen in de mate van participatie door cognitieve

gedragstherapie. Als het gevonden effect was bereikt door een medicijn was er minder verbazing geweest, maar ooit zal de medisch-wetenschappelijke wereld snappen waarom een psychologische behandeling effect heeft op het niveau van de spier…

Jos, wij waren een uniek team! Ik vind het geweldig dat je, door te assisteren bij mijn onderzoek, aangestoken bent met het onderzoeksvirus en nu zelf een promotietraject bent begonnen. Mede door jou bleven patiënten betrokken bij het onderzoek. Je hebt de unieke eigenschap goed om te kunnen gaan met uiteenlopende persoonlijkheden, van jong tot oud, uit alle windstreken. Dit heeft er zeker voor gezorgd dat er slechts één deelnemer is uitgevallen voor de metingen tijdens de studie. Ik wens je alle geluk bij het afronden van je promotieonderzoek en hoop nog vaak met je bij te kunnen kletsen, samen met Eva. Omdat ik me tijdens het onderzoek altijd erg gesteund heb gevoeld door je medewerking op alle vlakken, ben ik ook erg blij dat je mij ook tijdens de bijzondere dag van de promotie bij wil staan als paranimf.
Jessica, ook jij dank voor je nauwgezette hulp en betrokkenheid bij de start van het onderzoek.

Barbara, een groot deel van dit proefschrift is door onze samenwerking tot stand gekomen. En die verliep zo soepel als een pas gesmeerde ketting, ook nog na de publicatie van de artikelen, ondanks dat jouw promotie al was afgerond. Dank voor al je hulp! Hetzelfde geldt voor **Christine**.

Prof. Heerschap, beste **Arend**, dank voor al je hulp bij het publiceren van de MRI artikelen, die voor heel wat beroering in de medische wereld hebben gezorgd, maar die je steeds moeiteloos wist te weerleggen.

Dank aan de leden van het **FACTS-2-NMA** consortium, met een speciaal woord van dank voor **Fieke Koopman, Annerieke Groenestijn, Eric Voorn, Minne Bakker en Karen Schipper**, collega junior onderzoekers.

Elly van der Kooi en **Joke Kalkman**, dit proefschrift is "model based", het is gebaseerd op jullie onderzoeksbevindingen. Dank voor al jullie steun tijdens het traject. Jullie hebben mede de basis gelegd voor gedegen onderzoek en een goede band met de patiënten en de patiëntenvereniging.

Alle **therapeuten** van het onderzoek wil ik hartelijk danken voor hun inzet en enthousiasme: **Hein, Hans, Marcel, Ralph, Sanne, Liesbeth, Ton, Kevin, Jacques, Frank, Bea, Rob en Sandra.**

Dank aan de **revalidatieartsen** van de betrokken centra die belangeloos alle medewerking hebben verleend bij de inclusie van patiënten en faciliteren van de trainingen: **Reinout van Vliet, Dirk van Kuppevelt, Erwin Baars, Gerard van der Leeuw, Esther Kruitwagen, Manon Janse** en neuroloog **Anneke van der Kooi**.

Ron Meijer, een speciaal woord voor jou. Onze kennismaking ontstond door de keyboardlessen aan je zoon. Je enthousiasme voor het vak van Revalidatiegeneeskunde en de wetenschap inclusief de garantie dat ik het zou kunnen combineren met een sportcarrière heeft mijn keuze voor een specialisatie net op tijd weten te veranderen van de sport- naar de revalidatiegeneeskunde. Hier ben ik je nog altijd dankbaar voor.

Mijn collega **revalidatieartsen en arts-assistenten van Klimmendaal**. Dankzij jullie ga ik altijd met veel plezier naar mijn werk, wat ook een van de belangrijkste redenen was om jullie collega te blijven. Dank voor alle ruimte die ik krijg om mij te ontwikkelen én mijzelf te zijn. Zelfs wanneer ik onverhoopt, doordat mijn kleding nog thuis lag, een presentatie geef in mijn fietskleding, waar jullie niets eens van opkeken :)

De **collega onderzoekers** en **revalidatieartsen** van het RadboudUMC, in het bijzonder Imelda de Groot. Dank voor alle gezelligheid en hulp!

De neuromusculaire neurologen van het Radboudumc, **Joost Raaphorst**, dank voor het delen van je kennis tijdens mijn neuromusculaire etalagestage, **Nens van Alfen** en **Nicol Voermans**, dank voor de samenwerking bij de opzet van toekomstig onderzoek, wat ook geldt voor revalidatieartsen **Jan Groothuis**, **Viola Altmann**, ergotherapeute **Edith Cup** en logopedist **Bert de Swart**.

Doordat het proefschrift raakvlakken had met veel medische subspecialismen heb ik artikelen kunnen schrijven met auteurs vanuit de radiologie, neurologie, revalidatiegeneeskunde, longgeneeskunde, metabolomics en psychologie. Dank aan alle mede-auteurs van artikelen, voor zover niet eerder genoemd:
prof. Padberg, dr. Hendriks, dr. Van Alfen, dr. Wijkstra, prof. Kerstjens, dr. Meissner, dr. Deelder, dr. Mayboroda, dr. Morello J, dr. Nevedomskaya, dr. Pacchiarotta, dr. Pillen, dr de Rooy, dr. Kan, dr. Nabuurs, dr. Lindeman ɫ, dr Riphagen, dr. Van Middendorp, dr Rahbek, dr. Jansen, dr. Van den Engel-Hoek, dr. Zwarts, dr. Brehm en **dr. Beelen**.

Dank aan de **FSHD stichting** en **Spierziekten Nederland**, inclusief de **leden van de FSHD werkgroep**, met een speciaal woord van dank voor **Anke Lanser**, zij hebben steeds alle mogelijke medewerking op alle vlakken verleend.

"Mijn" teamleden van team 4 en Zintens, ik vind het geweldig hoe we samen aan het bouwen zijn aan goede behandelproducten. Ik bewonder jullie inzet, kennis en betrokkenheid. Een speciaal woord van dank voor "mijn" secretaresse Marian Bouwmeester, ik moet het eigenlijk veel vaker zeggen, maar ik ben enorm blij met jou als secretaresse, alleen jammer van die frequente buikpijn (van het lachen). Trap gerust nog geregeld op de rem, lach om mijn verstrooidheid, app me updates over de Olympische Spelen, of stuur me na een lange dag weg. Ik ben ook trots op jou! Danke Schön!

Mevrouw Jensma, beste Ytje, en nu ook mevrouw Agterdenbos, Esther: dank voor de geboden mogelijkheid om na mijn opleiding bij Klimmendaal te blijven en de ondersteuning op alle vlakken bij mijn promotie en het symposium. Ik vond en vind op Klimmendaal een unieke combinatie van een prettige werksfeer en een uitdagend werkklimaat, waar ik nog lang mijn steentje aan hoop bij te zullen dragen.

Eveline en Erica, jullie zijn gouden meiden. Met zijn drieën hebben we heel wat afgegiebeld tijdens de brainstormsessies. Het is uniek hoeveel uren tijd jullie aan de opmaak van dit proefschrift besteed hebben. Erica, je wist altijd precies weer te geven wat de kern van mijn boodschap was en hebt hierdoor ook inhoudelijk een bijdrage geleverd. Hierdoor heeft mijn proefschrift een geheel eigen uiterlijk gekregen. Waar Jos een grote rol had in de opzet en de uitvoering van het onderzoek, heb jij dit gehad in de vormgeving van het proefschrift. Super dat je mij ook bij staat als paranimf.

Lieve **Tessa**, een unieke vriendschap, ik weet nog goed hoe we vrienden werden tijdens het maken van appelmoes in de kleuterklas! We zijn met elkaar opgegroeid, hebben samen alle levensfasen doorlopen. Schreven elkaar wekelijks dikke brieven, uren spellen spelen, spraken cassettebandjes vol, samen naar de Efteling en Parijs, gingen studeren, koffie rondbrengen als vakantiewerk. Ik hoop hier straks als twee omaatjes tevreden op terug te kijken!

Lieve **Mebeline**, grappig hoe een vriendschap begint door bij toeval naast elkaar te zitten tijdens een eerste hoorcollege. Met jou deel ik een liefde voor geneeskunde en sport en nu ook in de zorg voor patiënten met niet-aangeboren hersenletsel. Jammer dat je niet bij de promotie aanwezig kunt zijn, maar ik weet dat je dat in gedachten wel bent.

Edwin en José, met Joost kreeg ik er gelijk leuke vrienden bij. In die mate, dat Joost een keer verbaasd zei dat ik jullie vaker spreek dan hijzelf ;) Ik hoop dat ik samen met José nog vaak afspraken op verzoek van de heren mag maken!

Lieve **Mireille**, het is alsof we elkaar al ons hele leven kennen, terwijl onze vriendschap pas een paar jaar bestaat. Het is zo fijn om geregeld over en weer stoom af te blazen tijdens fysieke activiteiten en het wederzijdse begrip te voelen en uiten. Ik hoop dit nog heel lang te kunnen blijven doen!

Lieve **Debbie**, we hebben elkaar leren kennen tijdens geneeskunde. Jammer dat je niet meer in de buurt woont, maar als we elkaar bellen, halen we de schade ruimschoots in!

Hanneke en **Eric**, dank voor jullie vriendschap, stiekem hoop ik jullie vaker weer in Nederland te zien! Ik waardeer het zeer dat Hanneke een bijdrage levert aan het symposium.

Kaori Muratsubaki and the Muratsubaki family, my forever friend and second family. We know each other for already 17 years now since we first met in Izu, Japan during a finswimming open water competition. I hope we can continue visiting our houses and home countries again and again! Sayonara!

Zoals vermeld in de stellingen: 'Het leven is als fietsen, om overeind te blijven moet je blijven bewegen'. De sport heeft me tijdens dit zware traject overeind gehouden. Maar zeker ook mijn medesporters:
Mede triatleten van **KIJANI**, dank voor jullie vriendschap en sportieve uitdagingen. Mijn prestaties voor het team in het laatste seizoen werden sterk gedrukt door alle life-events, inclusief de promotie, maar ik heb daarvoor vanuit jullie enorm veel begrip ervaren.
Datzelfde geldt voor de leden van **Pontos**, ondanks mijn onregelmatige opkomst bij de trainingen, met tijdens de dienst mijn waterdichte mobiele telefoon op het startblok, was ik altijd welkom in het wedstrijdteam. Tot slot de **RZC'ers**. Onvoorstelbaar hoe Joost en ik ons in zo'n korte tijd thuis zijn gaan voelen bij deze zwemclub. Tegenwoordig zelfs met triatlonafdeling, dus we gaan nog lang niet weg!

Lieve grote broers **Patrick en Marc**. Een klein meisje, maar ook een volwassen vrouw, kan niet blijer zijn dan met twee grote broers die trots zijn op, en beschermend naar hun kleine zusje zijn. Ik ben ook enorm trots op jullie! **Ilonka, Mabel, Siméon en Michon**, "mede Voetjes" dank voor alle liefde, gezelligheid en de onvoorwaardelijke familieband! Dat we nog maar snel en vaak op voetenweekend gaan en dan veel onhandige 'voetjes' aan de eettafel mogen maken!

Jan, Thea, Imke, Magiel, Mats, Jurre en Mare. Ze noemen het de koude kant, maar ik voel alleen maar warmte, en dat komt niet alleen door de houtkachel van Jan!

Lieve **papa en mama**, woorden zijn bij lange na niet voldoende om de liefde te omschrijven die ik voor jullie voel. Jullie hebben mij zoveel gegeven, dat kan ik nooit in gelijke mate teruggeven. Als nakomertje werd ik overstelpt met liefde en tijd. Ik weet zeker dat dit in grote mate heeft bijgedragen aan mijn 'prestaties' in studie, werk en sport. Waar jullie enorm trots op zijn. Van twee kanten heb ik leergierigheid, doorzettingsvermogen, het belang van fysieke activiteit maar ook eigenwijsheid meegekregen. Dit proefschrift is daar een resultaat van, en daarom aan jullie opgedragen.

Lieve **Joost**, onze relatie duurt net iets langer dan mijn promotietraject. Je kent mij bijna niet anders dan als promovenda! Partner van een promovenda zijn is als de stoker op een tandem, je hebt wel enig idee waar het naar toe gaat, maar onderweg zie je niets en de koers kan ineens veranderen. Takken die de schouder van de captain raken treffen de stoker vol in het gezicht. Je trapt maar mee om de vaart er in te houden, maar kan zelf niet remmen en sturen. Je kunt alleen mee- of tegenhangen. Soms lukt het daarmee de koers te wijzigen of onderuit te gaan, en dan blijkt dat je toch nog meer invloed hebt dan je denkt, "achterop". Communiceren is daarbij van levensbelang. Ze zeggen altijd: "wherever your relationship is going, a tandem will bring you there faster". Ik ben ervan overtuigd dat minimaal hetzelfde geldt voor een promotietraject. Dat wij dit nu beiden én samen hebben doorstaan zegt mij meer dan voldoende! Mijn liefde voor het onderzoek gaat verder maar mijn liefde voor jou is niet in woorden te omvatten. Schat, we gaan weer naar het grote blad!

1983

2001

2005

2007

2008

2016
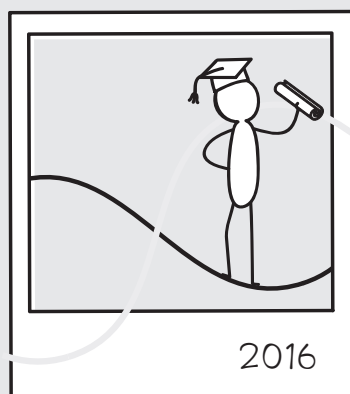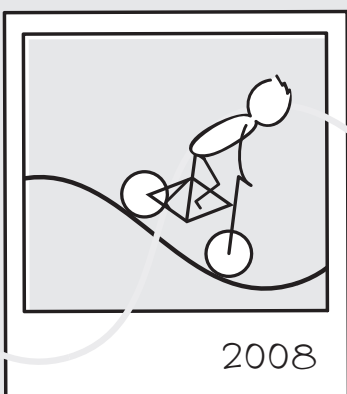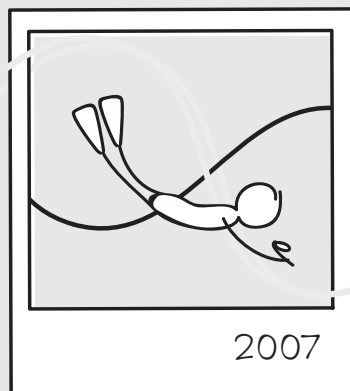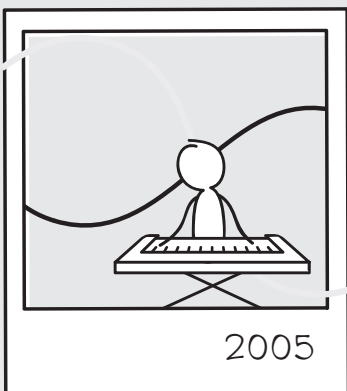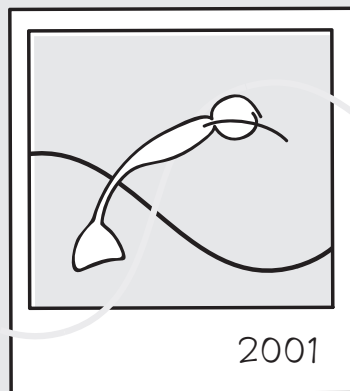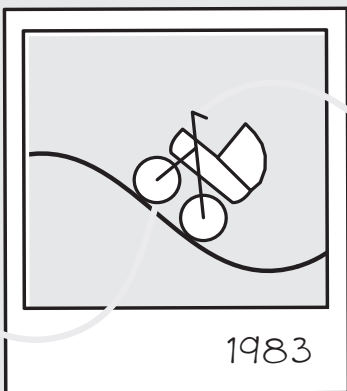
CURRICULUM VITAE

BIOGRAFIE

Nicole Voet is op 15 april 1983 in Nijmegen geboren. Ze groeit op in Wijchen en sluit het Gymnasium op het Dominicus college in Nijmegen cum laude af. In 2001 start zij vervolgens haar studie geneeskunde in Nijmegen. In 2002 behaalt zij haar propedeuse cum laude. In 2005 schrijft zij tijdens een keuzevak mee aan een wetenschappelijk artikel waarbij haar interesse voor de wetenschap wordt gewekt. Tijdens haar coschappen maakt zij per toeval kennis met de revalidatie als zij keyboardles geeft aan de zoon van haar latere opleider. Het blijkt dat de revalidatiegeneeskunde perfect aansluit bij haar, tijdens het doctoraal examen geuite, wens om chronische aandoeningen te "genezen" met sport en bewegen.

Na het afronden van haar studie in 2007 werkt zij een half jaar als arts in revalidatiecentrum Klimmendaal te Arnhem. In 2008 wordt zij aangenomen als AIOSKO revalidatiegeneeskunde (arts in opleiding tot specialist en klinisch onderzoeker) in het opleidingscircuit Radboud universitair medisch centrum (Radboudumc) te Nijmegen en Klimmendaal. Zij start in 2008 met de voorbereidingen van het FACTS-2-FSHD onderzoek.

Het FACTS-2-FSHD onderzoek (acroniem voor Fitness And Cognitive behavioural TherapieS/for Fatigue and ACTivitieS in FSHD) werd gesubsidieerd door het Prinses Beatrix Spierfonds, ZonMw, het Revalidatiefonds, Revalidatie Nederland en Global FSH en was het eerste, op een theoretisch model gebaseerde, gerandomiseerde klinische onderzoek naar het effect van aerobe training en cognitieve gedragstherapie op ervaren vermoeidheid bij patiënten met FSHD. De resultaten hiervan staan beschreven in dit proefschrift.

Het heeft geleid tot 16 wetenschappelijke publicaties en vele (inter)nationale presentaties en deelname in meerdere (inter)nationale werkgroepen. In maart 2015 heeft zij haar opleiding tot revalidatiearts afgerond, waarna zij werkzaam is op de afdeling Na Hersenletsel en Zintens arbeid en gezondheid in Klimmendaal. Haar aandachtsgebieden zijn cognitieve revalidatie, bewegen en sport, en arbeid. Ze participeert nog steeds, in nauwe samenwerking met het Radboudumc, aan wetenschappelijk onderzoek bij neuromusculaire aandoeningen.

Nicole Voet woont samen met Joost Christiaans in Wageningen.

BIOGRAPHY

Nicoline (Nicole) Voet was born on April 15th 1983 in Nijmegen, the Netherlands. She grew up in Wijchen. In 2001 she passed secondary school (Dutch Gymnasium) summa cum laude after which she commenced her study medicine. In 2002, she received her propaedeutics summa cum laude. During her study, she already published an article in a peer reviewed journal. During her internships, she switched her preference from sports medicine to rehabilitation medicine, because of her wish, as she pronounced after receiving her Master's degree, to "cure chronic diseases with exercise".

After her graduation in 2007, she worked for 6 months in rehabilitation center Klimmendaal in Arnhem. In 2008 she started her PhD project as a primary investigator of the multicenter, randomized clinical trial the FACTS-2-FSHD study.

The FACTS-2-FSHD study (acronym for Fitness And Cognitive behavioral TherapieS/for Fatigue and ACTivitieS in FSHD) was funded by the Prinses Beatrix Spierfonds (PBF), the Netherlands Organization for Health Research and Development (ZonMw), and the FSHD Global Research Foundation and was the first theory-based randomized clinical trial that evaluated the effect and the maintenance of effects of aerobic exercise therapy and cognitive behavioral therapy on the reduction of chronic fatigue in patients with FSHD. The results of this study are described in the present thesis.

In 2009, she started her residency at the Radboud University Medical Center in Nijmegen (Radboudumc). She alternately worked at the Radboudumc and Klimmendaal in Arnhem. After finishing her residency in 2015, she started working as a rehabilitation physician in Klimmendaal, at the in- and outpatient brain injury department and, a couple of months later, at the department "Zintens" for vocational rehabilitation. Her specialty is cognitive rehabilitation, vocational rehabilitation, and exercise training. She is continuing her research in neuromuscular disorders at Klimmendaal, in close co-operation with Radboudumc.

Nicole Voet lives together with Joost Christiaans in Wageningen.

SPORTCARRIERE

Vanaf haar 12e jaar beoefent Nicole topsport. Na het behalen van een 12e plaats op de World Games tijdens de 400 meter vinzwemmen in Japan in 2001 krijgt ze de Olympische B status bij het NOC*NSF waardoor het mogelijk was een topsportcarrière te combineren met haar studie geneeskunde. In 2003 wordt ze Europees kampioen met het onderwaterhockeyteam en in 2007 2e op het WK open water vinzwemmen.

In 2010 start zij met het beoefenen van triatlons met vanaf haar eerste wedstrijd een reeks podiumplaatsen tot gevolg tijdens zowel triatlons, loopwedstrijden als tijdritwedstrijden. Tot haar beste prestaties behoren de winst tijdens het Nederlands Kampioenschap tijdrijden voor rijders zonder licentie in 2012 en een top 10 plaats tijdens het NK triatlon Olympische afstand in 2013.

Momenteel neemt ze met triatlonteam KIJANI deel aan de Eredivisie triatlon wedstrijden.

SPORTS CAREER

From the age of 12 years, Nicoline is involved in top sport. Because she finished 12th at the 400 meter finswimming in the World Games in Japan, she received support from the Dutch Olympic committee and was able to combine her study with top sport. In 2003 she became European champion with the Dutch underwaterhockey team and in 2007 she gained a second place at the open water finswimming World Championships.

From 2010 she participates in triathlons and, since her first competition, she frequently finishes on the podium during triathlons, running- as well as time trial races. Her best results are a first place at the Dutch National time trial championships for semi-professional cyclists in 2012 and a top 10 finish during the Olympic Distance Triathlon National Championships in 2013.

Currently, she participates in the triathlon competitions of the primary league with her triathlon team KIJANI.

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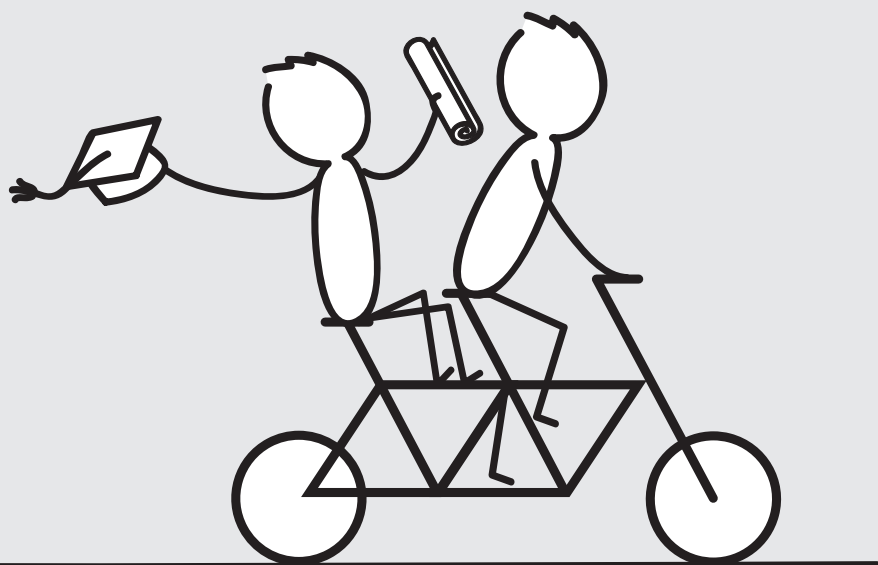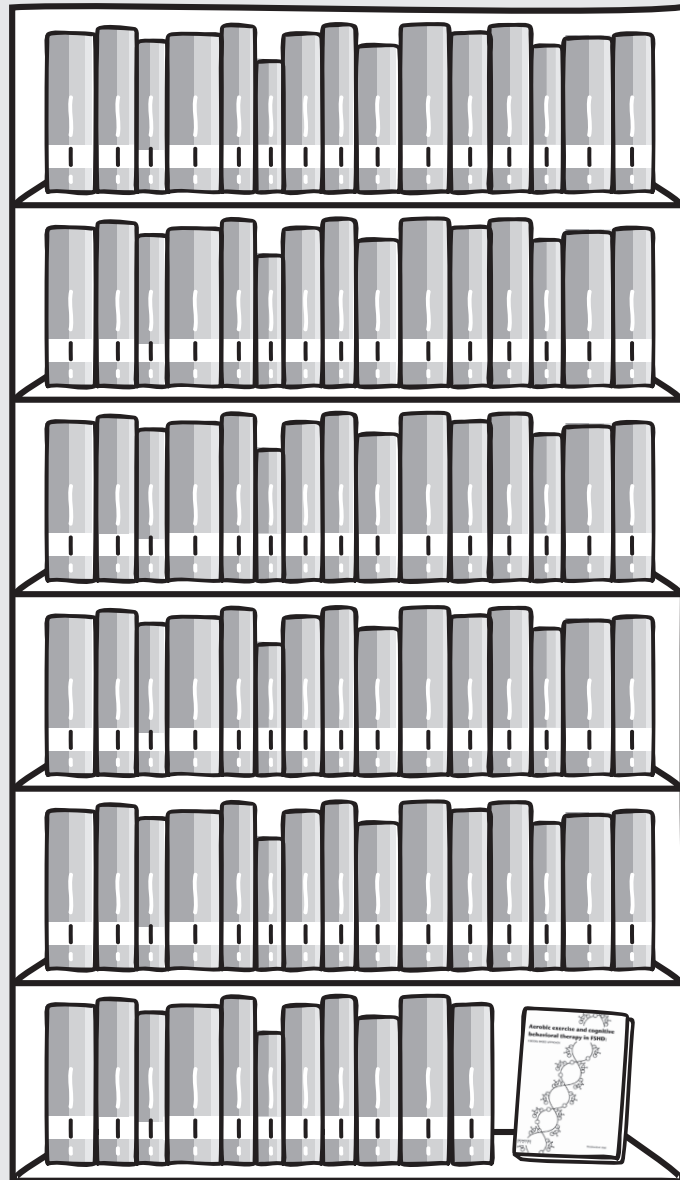
SUBMITTED ARTICLES

Koopman S, Brehm M, Beelen A, **Voet N**, Bleijenberg G, Geurts A, Nollet F et al. Cognitive behavioral therapy for reducing fatigue in post-polio syndrome compared to facioscapulohumeral dystrophy: the role of fatigue related cognitions.

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