Trunk Muscle Impairment and Pain in Myotonic Dystrophy type 1
Association to CTG size and Function

Gro Solbakken
Trunk Muscle Impairments and Pain in Myotonic Dystrophy type 1 Association to CTG size and Function

Table of Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>TABLE OF CONTENTS</td>
<td>1</td>
</tr>
<tr>
<td>LIST OF ABBREVIATIONS</td>
<td>2</td>
</tr>
<tr>
<td>ACKNOWLEDGEMENT</td>
<td>3</td>
</tr>
<tr>
<td>NORSK SAMMENDRAG</td>
<td>5</td>
</tr>
<tr>
<td>THESIS SUMMARY</td>
<td>6</td>
</tr>
<tr>
<td>ARTICLES IN THE THESIS</td>
<td>8</td>
</tr>
<tr>
<td>1. INTRODUCTION</td>
<td>8</td>
</tr>
<tr>
<td>1.1 MYOTONIC DYSTROPHY TYPE 1 (DM1)</td>
<td>8</td>
</tr>
<tr>
<td>1.1.1 Diagnosis</td>
<td>9</td>
</tr>
<tr>
<td>1.1.2 Genetic cause of DM1</td>
<td>10</td>
</tr>
<tr>
<td>1.1.3 Prevalence</td>
<td>11</td>
</tr>
<tr>
<td>1.1.4 Classification and subgroups</td>
<td>11</td>
</tr>
<tr>
<td>1.2 SKELETAL MUSCLES</td>
<td>12</td>
</tr>
<tr>
<td>1.2.1 Fiber types and plasticity</td>
<td>12</td>
</tr>
<tr>
<td>1.2.2 Aging and disease, impact on fiber type</td>
<td>13</td>
</tr>
<tr>
<td>1.2.3 Plasticity due to exercise</td>
<td>13</td>
</tr>
<tr>
<td>1.3 MYOPATHY IN DM1</td>
<td>13</td>
</tr>
<tr>
<td>1.4 MYOTONIA IN DM1</td>
<td>13</td>
</tr>
<tr>
<td>1.5 MUSCLES INVOLVED IN DM1 ADULT FORMS</td>
<td>14</td>
</tr>
<tr>
<td>1.5.1 Trunk muscles</td>
<td>14</td>
</tr>
<tr>
<td>1.6 OTHER ORGS AND SYSTEMS INVOLVED</td>
<td>15</td>
</tr>
<tr>
<td>1.7 FATIGUE AND DM1</td>
<td>15</td>
</tr>
<tr>
<td>1.8 PAIN AND DM1</td>
<td>16</td>
</tr>
<tr>
<td>1.9 BALANCE AND FALLS AND DM1</td>
<td>16</td>
</tr>
<tr>
<td>1.10 RESPIRATION AND DM1</td>
<td>16</td>
</tr>
<tr>
<td>1.11 TREATMENT AND GUIDELINES FOR DM1</td>
<td>17</td>
</tr>
<tr>
<td>1.12 CLINICAL CHALLENGES LEADING UP TO THIS THESIS</td>
<td>18</td>
</tr>
<tr>
<td>2. THESIS AIMS</td>
<td>18</td>
</tr>
<tr>
<td>2.1 MAIN AIMS</td>
<td>18</td>
</tr>
<tr>
<td>2.1.1 Aims of study I</td>
<td>18</td>
</tr>
<tr>
<td>2.1.2 Aims of study II</td>
<td>18</td>
</tr>
<tr>
<td>2.1.3 Aims in study III</td>
<td>19</td>
</tr>
<tr>
<td>2.1.4 Aims of study IV</td>
<td>19</td>
</tr>
<tr>
<td>3. MATERIALS AND METHODS</td>
<td>19</td>
</tr>
<tr>
<td>3.1 DESIGN, PARTICIPANTS AND INCLUSION</td>
<td>19</td>
</tr>
<tr>
<td>3.1.1 Inclusion to the separate studies</td>
<td>20</td>
</tr>
<tr>
<td>3.2 COOPERATION</td>
<td>23</td>
</tr>
<tr>
<td>3.3 MEASURES</td>
<td>24</td>
</tr>
<tr>
<td>3.3.1 Motor function measures and questionnaires</td>
<td>24</td>
</tr>
<tr>
<td>3.3.2 Information from medical files</td>
<td>27</td>
</tr>
</tbody>
</table>
List of abbreviations

DM1: Myotonic Dystrophy type 1
DH VV-HF: Drammen Hospital Vestre Viken Hospital Trust
ASD: Autism spectrum disorder
AQ: Autism Spectrum Quotient
BAI: Beck’s Anxiety Inventory
BDI: Beck’s Depression Inventory
BiPAP: Bilevel Positive Airway Pressure
BMI: Body Mass Index
CNS: Central nervous system
CTG: Cytosine Thymine Guanine trinucleotide repeat
DMPK: Myotonic Dystrophy Protein Kinase gene
EMG: Electromyography
FVC: Forced Vital Capacity
IENFD: Intraepidermal Nerve Fiber Density
MMT: Manual Muscle Strength Tests
MRC: Medical Research Council’s MMT score
MRI: Magnetic Resonance Imaging
6MWT: Six Minute Walk Test
NRS: Numeric Rating Scale
OUH: Oslo University Hospital
RMI: Rivermead Mobility Index
SPSS: Statistical Package for the Social Sciences
TUG: Timed Up & Go
UNN: University Hospital of North Norway

Acknowledgement

This work was carried out at the department of Neurology Rheumatology and Rehabilitation at Drammen Hospital, the department of Neurology at Oslo University Hospital, the section of Neurophysiology at the University Hospital of North Norway and the department of Diagnostic Imaging at Drammen Hospital. This study was funded with a full PhD grant by the foundation of Sophies Minde, partly by Vestre Viken Hospital Trust and the Unit for Inborn and Hereditary Neuromuscular Disorders (EMAN) Oslo University Hospital. The patient’s organization “Foreningen for muskelsyke”, supported the study from the start. The faculty of medicine allowed me to follow their excellent PhD program. My sincerely gratitude to you all.
I like to thank all who participated in this work, in particular:
- Each participant with DM1 and every control, you enabled this study.
- My colleagues in the muscle clinic at Drammen Hospital: MD Tormod Hagen and MD Gunnar Hansen, you have been crucial in the medical assessment of the participants, MSc socionom Torunn Dahl Eikeland, you managed the muscle clinic in an excellent way, and collected important information about quality of life. Our interdisciplinary work in the muscle clinic has guided the goals and implementation of the present project, and I am sincerely grateful for your enduring participation and friendship.
- My main supervisor MD PhD Kristin Ørstavik Consultant in Neurology and Clinical Neurophysiology, Head of Unit for Inborn and Hereditary Neuromuscular disorders (EMAN) and Section for Rare Neuromuscular disorders, Department of Neurology Oslo University Hospital. Thank you for sharing clinical, social and scientific expertise and, friendly support, and for availability at all times. Thanks for including me in your extensive network in the field of
neuromuscular disorders and to your unit EMAN with all its highly competent employees. For interesting discussions, for several dinners, for initiating national and international interaction. For your hands-on work in examining patients and the writing process. This could not have been done without you.

- My co supervisors Professor MD Jan Frich and Professor MD Espen Dietrichs, you both contributed with important scientific and clinical expertise of great value for this project. You always responded with interesting and to the point comments. Your contribution to design and helps with writing the papers, ensured high scientific level of this work. My local co supervisor MD PhD Anne Froholdt, you contributed with expertise in physical medicine, important comments, support and enthusiasm. I am grateful and have learned a lot from you all. Hopefully you will be interested in continued cooperation.

- MD Bård Bjørnarå, MD PhD Eva Kirkhus and BSc Bac Nguyen, your expert knowledge ensured the high quality of the MRI study. -MD PhD Sissel Løseth, your experience and expertise in neurophysiology, was invaluable for the pain study. Thank you all for these very important and interesting contributions.

- My college Charlotte Ramdahl for inspirational conversations, and for reliability scoring of the strength assessments. -The psychologists assessing participants: Hanne Simensen, Anne Well.

- My fellow research colleges: Tove Tveitan Borgen, Marte Roa Syvertsen, Mari Wold Henriksen, Ida Stenshorne, and Cecilia Smith Simonsen, you contributed to an inspiring, scientific environment. Our previous head of research Jeanett Koht was central in developing this scientific environment.

- To all my colleagues who asked about progression and showed interest.

- Dag Fosmark, Sean Wallace and Cecilia Smith Simonsen for valuable contribution on linguistic aspects and proof reading of papers and the thesis.

- Much appreciated statistical support has been given by Christian Page.

- Many leaders facilitated the project: Especially thanks to May-Britt Bunes, your support was necessary. Kari Krum Bang, Elisabeth Weatherup and Mai Bente Myrvold, thank you for great support.

- To my extended family and friends. To my daughter Sofie and Åse Ingvill, and my son in law Peder, for exiting discussions and curiosity. To my husband Terje for sharing your scientific knowledge, and for helping with the horses when I was busy. To the newest member of the family Hennie, for all your love and joy, capturing the moment. I love you all!
Norsk sammendrag

**Bakgrunn:** Dystrofia Myotónica type 1 (DM1) er en arvelig, heterogen og langsomt progredierende nevromuskulær sykdom med multiorganaffeksjon. Det finnes fire undergrupper av DM1: kongenital form, barneform og to voksenformer. Vi forsker på voksenformene.

En viktig bakgrunn for denne avhandlingen var kliniske funn og observasjoner gjort ved rutinemessige polikliniske oppfølginger av voksne personer med DM1, som indikerte pareser i mave- og ryggmuskulatur (trunkus), samt forekomst av smerte. Begge fenomenene har fått liten vitenskapelig oppmerksomhet. Pareser i mave og ryggmuskulatur var motstridende til den etablerte oppfattelsen av hvordan DM1 progredierte. Muskellaaffeksjon hos voksne personer med DM1 har vært forventet å starte distalt i ekstremitetene, med en langsom progresjon til proksimale deler av ekstremiteten. Smerte hos personer med DM1, har høvdsakelig vært forsket på gjennom utsending av spørreskjemaer, til grupper med ulike nevromuskulære diagnoser. Hoved symptomene som skiller DM1 fra Dystrofia Myotónica type 2 har i litteraturen vært beskrevet som fravær av smerte, samt distalt lokaliseret myopati i DM1.

**Hensikt:** Vårt overordnede mål med denne studien var å undersøke smerter, samt muskulatur i trunkus hos personer med voksenformene av DM1. Vi undersøkte om og hvordan muskulaturen i trunkus var affisert og om pareser og eventuelt myopati i abdominal og rygg- muskulatur var relatert til størrelsen på genfeilen som gir DM1 (CTG størrelse), sykdomsvarighet, og motorisk funksjon. Dernest, undersøkte vi smerte, og hvorvidt smerte i gruppen var relatert til kjønn. Videre undersøkte vi hvorvidt smerte var assosiert til CTG størrelsen, sykdomsvarighet, livskvalitet, og motorisk og psykologisk funksjon. Til slutt kartla vi om nevropati og nevropatisk smerte forekom hos personer med DM1.

**Metode:** Dette er en tverrsnittstudie, datainnsamlingen er gjennomført med et bredt sett av kliniske mål kombinert med spørreskjemaer, så vel som en MR kasus-kontroll-studie. Flere profesjoner og spesialiteter deltok i datainnsamlingen, og inklusjonen ble gjennomført ved tre forskjellige sykehus. Statistiske analyser av sentraltendenser, variasjon og korrelasjoner, gruppeforskjeller, samt regresjonanalyser ble gjennomført. 50 personer med DM1 og 20 friske kontroller, matchet for alder og kjønn, ble inkludert. I tillegg fikk vi tilgang til et datasett, basert på 106 friske kontroller, til et av målene i nevropatistudien.

**Resultat:** I denne studien har vi dokumentert relativt tidlige og alvorlige pareser, samt myopatiske forandringer i rygg og abdominal muskulatur hos voksne personer med DM1.


**Thesis summary**

**Background:** Myotonic Dystrophy type 1 (DM1) is a progressive, hereditary neuromuscular disorder with multi-organ involvement. DM1 is highly heterogeneous. Clinical observations of trunk muscle involvement and pain in the routine follow-up of DM1 adult patients in the outpatient setting, provided important background information for this thesis. Both symptoms had received little scientific attention in the DM1 adult forms, when we started our study. The observed trunk muscle impairment was in contrast to the established view of the progression of...
the disorder. Myopathy was expected to start distally and slowly progress to proximal muscles in the extremities. Pain was mainly investigated by surveys in mixed groups of neuromuscular diseases. The main symptoms differentiating DM1 from myotonic dystrophy type 2 were considered to be the absence of pain and more distal muscle impairment in DM1 compared to Myotonic Dystrophy type 2.

**Aims:** Our aim was to investigate if and how trunk muscles were affected in adult patients with DM1. Furthermore, we wanted to ascertain if trunk muscle impairment was related to CTG size, disease duration and motor function. And finally, we sought to investigate pain, and asked if pain was related to gender, CTG size, disease duration, quality of life and motor and psychological function. If neuropathy and neuropathic pain was present, was our last question.

**Method:** Our study design was cross sectional and involved a broad set of clinical assessments combined with self-reports, as well as one MRI case-control study. Several professions and specialities participated in the data collection, and inclusion was spread across three different hospitals. Statistical analysis involved descriptions of central tendencies, variation and relations, as well as regression analysis. A total of 50 adult form persons with DM1 and 20 healthy age and gender-matched controls were included. We also were given access to data from 106 healthy controls to compare with data from persons with DM1 included in the neuropathy study.

**Results:** The current study has documented relatively early and severe impairments and myopathy of the trunk muscles. The trunk muscle impairments were related to CTG size, disease duration, mobility, balance and respiration. By MRI large case-control differences were availed for muscle fat infiltration and atrophy and edema. These myopathic changes were associated to motor function (mobility and balance) and respiration (forced vital capacity) in the DM1 group. We also found high frequencies of chronic pain related to CTG size, disease duration, fatigue, respiration and quality of life. Furthermore, significant gender differences for pain frequency, intensity and locations, as well as how pain related to other symptoms, were documented. The most frequent pain location was the lower back, the neck and palmar side of the hands. Low back pain was more prevalent in woman than men. Together large and small fiber neuropathy was present in 50% of the 20 participants in the neuropathy study. 30% reported pain qualities in line with neuropathic pain, and half of these (15%) also had sensory deficits and findings indicating small or large fiber neuropathy. Significant lower intraepidermal nerve fiber density was present in the DM1 group, compared to healthy controls.
Conclusions: Relatively early and severe impairments, and myopathy of trunk muscles may be present in adult forms of DM1. The trunk muscle impairments were associated to CTG size, disease duration, respiration, mobility and balance. The documented myopathy; muscle fat infiltration and atrophy may be caused by DM1. High frequencies of pain and gender differences for pain, related to different DM1 symptoms, are documented. Neuropathy might be part of the pain in DM1. The results underscore that both trunk muscles and pain, with its associated symptoms, should be examined regularly in the clinical setting. Trunk muscle function, as well as trunk muscle myopathy, should be considered as future outcome measures. Gender should be accounted for in future studies of pain in DM1.

Articles in the thesis


1. Introduction

1.1 Myotonic Dystrophy type 1 (DM1)

DM1 is a neuromuscular disorder, which is a group of inherited disorders affecting some part of the neuromuscular unit. Main categories are neuropathies and myopathies, and common clinical findings include impaired muscle strength and motor function [1].
Myotonic Dystrophy type 1 (DM1) is a slowly progressive myopathy affecting muscles, but also several other organs and systems such as the eyes, the heart, the brain, peripheral nerves, the hormonal and digestive system. DM1 is highly heterogenous and may lead to several clinical manifestations. The disease is divided into four different subgroups depending on time of onset [2, 3]. Not all patients show motor impairment or muscle weakening as the first symptom. Cataract, myotonia and cardiac arrhythmia are also possible onset symptoms [2, 3].

Facies myopathic, frontal balding, nasal speech, muscle wasting mainly in the distal part of the extremities, and myotonia are considered classical symptoms of DM1 and were first described by Hans Gustav Wilhelm Steinert in 1909 [4]. DM1 is therefore also called Steinert’s disease [5]. See figure 1.

*Figure 1. Portrait of Hans Gustav Wilhelm Steinert (From Wikipedia, the free encyclopedia)*

1.1.1 Diagnosis

Before genetic testing became available, diagnosis was based on clinical signs and symptoms from the muscles involved in DM1, which include myotonia, impaired muscle strength, electromyography (EMG), creatine kinase and muscle biopsies findings and a positive family history. Today, genetic testing is widely available and integral in confirming the diagnosis [2].
1.1.2 Genetic cause of DM1

DM1 is an autosomal dominantly inherited disease and belongs to a group of genetic disorders with unstable repeat expansions. Other known repeat expansion disorders are Huntington’s disease and Fragile X syndrome [6].

The genetic cause of DM1 was established in 1992: an unstable repeat expansion of the cytocine-thyamine - guanine (CTG) trinucleotide complex in the 3’ untranslated region of the Myotonic Dystrophy Protein Kinase (DMPK) gene, located at chromosome 19q13.3 [7]. Unaffected individuals have between five and 37 CTG repeats. Premutations, which lead to symptomatic offspring, demonstrate between 38-49 repeats, while full mutations, which almost always lead to symptoms, have between 50 and several thousand [8]. A relationship between the expansion size and the severity of the disease is documented in a substantial amount of papers over the years. However, some patients do not present symptoms according to their CTG repeat size, and caution must be exercised when evaluating individual subjects [9-11].

There are three important phenomena regarding CTG size in DM1: 1.) Anticipation, which almost always means increased amounts of CTG repeats in affected offspring [12], 2.) The instability of CTG repeats continues in the individual throughout their life-time, which most often leads to increased repeat size and 3.) Mosaicism, where the CTG levels vary in different tissues, e.g. it is higher in muscle tissue than in white blood cells. The instability and mosaicism influence the relationship between CTG size and clinical symptoms. The instability is influenced by sex. The congenital form is mainly from a DM1 affected mother, while low levels of CTG repeats from a father lead to a larger increase of CTG repeats in the offspring than low levels from the mother [13-15]. In addition, interrupted CTG repeats with GGC, CCG or CTC are seen in 5% of patients, and may have some role in delaying the onset of symptoms [10, 16].

The normal product of the DMPK gene is a protein kinase, which acts as a molecular switch and is involved in a range of cellular pathways. These kinases are primarily localized in specialized cell structures in the heart and skeletal muscle. The fact that the CTG expansion is in an untranslated region (not in the protein coding part), and that other mutations in the DMPK gene does not lead to DM1 symptoms, has led to some confusion about the molecular mechanisms behind the multisystemic features of DM1. In addition to the effect on the DMPK gene product itself, the expansion may alter the shape of the DNA in this region, thereby altering the expression of neighboring genes, including the DMPK gene. Today, most evidence supports an RNA-
mediated mechanism of DM1, with toxic effects of the expanded CUG - RNA accumulated both in the nucleus and cytoplasm. Studies indicate that this disrupts splicing of other genes [17-19].

### 1.1.3 Prevalence

DM1 is the most frequent hereditary muscle disease amongst adults, with a world-wide prevalence of 12/100 000. It varies geographically and is more frequent in Finland, Northern Sweden, Canada and western Europe. It is less frequent in Japan and India, and almost absent on the African continent [20]. We do not know the prevalence in Norway. One recent study, a screening of newborns in New York, suggests the prevalence may be higher than the current estimate [21].

### 1.1.4 Classification and subgroups

The different subgroups of DM1 are categorized by age of symptom onset. The subgroups have core clinical features, and a certain range of CTG repeats. These sub groups are not to be seen as distinct groups, but rather as a continuum. Until recently these were: 1.) congenital form with onset in the first year of life, 2.) childhood form with onset between 1 and 10 years of age, 3.) classic form, with onset between 10 and 40 years of age, and 4.) late adult form, with onset after 40 years of age [3, 11, 22, 23]. For details, see Table1.

### Table 1. Presentation of the DM1 classification

<table>
<thead>
<tr>
<th>DM1 Type</th>
<th>Age years</th>
<th>Core symptoms</th>
<th>CTG repeats</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital</td>
<td>0-1</td>
<td>Decreased fetal movements, hypotonia, respiratory failure and feeding problems, need of intensive care. Cognitive impairment, delayed motor milestones, later in life adult symptom presentation.</td>
<td>&gt;1000</td>
</tr>
<tr>
<td>Childhood</td>
<td>1-10</td>
<td>Delayed motor milestones, cognitive impairment, later in life adult symptom presentation.</td>
<td>50-1000</td>
</tr>
<tr>
<td>Classic</td>
<td>10-40</td>
<td>Myotonia, decreased muscle strength in the extremities, impaired motor function, cataract, respiratory affection, heart affection, bowel and intestinal involvement, endocrine involvement. Cognitive impairment, avoidant personality, social communication difficulties.</td>
<td>50-1000</td>
</tr>
<tr>
<td>Late adult</td>
<td>&gt;40</td>
<td>Cataracts, myotonia.</td>
<td>50-100</td>
</tr>
</tbody>
</table>
In 2019, at the International Dystrophy Myotonic Congress 12 (IDMC12) in Gothenburg, a new set of subgroups were suggested. The new classification introduced a juvenile form, with onset between 10-20 years of age, which mainly differs from the adult forms by more frequent mild cognitive impairment. Two adult forms were suggested: 1) adult form with onset between 20-40 years of age and main symptoms like the old classic form, and 2) late adult form with onset after 40 years of age, presenting with symptoms like the previous late-onset form [24].

In this thesis, we use the initial classification of four subgroups as presented in table 1. For simplicity, we refer to the forms with onset after 10 years of age as adult form.

1.2 Skeletal muscles

Skeletal muscles are contractile tissue that may shorten, lengthen or work statically [1]. Muscles are responsible for moving and balancing the body. The latter is a demanding task given the small base of support of the erect human body. Muscles do not work alone, but in synergy. Some muscles stabilize joints and control posture, while others are mobilisers. Which muscles are involved in solving a specific task varies depending on personal factors, the task itself and context [25]. Muscle function may be tested in different ways. Muscle strength may be measured by manual muscle strength tests (MMT) according to the Medical research council’s (MRC) 0-5 scoring system [26], or by a quantitative muscle strength test, which reports strength performance in kilos or newton. Muscle strength testing follow procedures that intend to measure primary mover muscles isolated [27]. However, another way of measuring muscle function is by performing functional tests, which mimic normal activity, like walking, balance tests, gross motor and fine motor movements [25]. Questionnaires addressing different activities or symptoms involving motor function is another possible assessment of muscle function.

1.2.1 Fiber types and plasticity

Muscles are built up of bundles of multi nuclear muscle fibers. In humans there are two main groups of fibers, which may be categorized according to function and metabolism: Type I are slow twitch, low force and fatigue resistant fibers that are dependent on oxidative metabolism. Type II are fast twitch, high force and quickly fatigued fibers, dependent on glycolytic metabolism. There are also intermediate fibers with both glycogenic and oxidative metabolism [28, 29]. All muscles are composed of both type I and type II fibers spread throughout the muscle.
However, the ratio of fast or slow fibers differs in different muscles [28]. In trunk muscles, there is a higher percentage of type I muscle fibers compared to type II [30, 31].

1.2.2 Aging and disease, impact on fiber type
The composition of muscle fibers in a muscle changes as part of normal aging. Degeneration of fast fibers occurs first. Selective muscle fiber type atrophy is also documented in some inherited myopathies. Muscle fiber type II atrophy is more prevalent in Duchenne, Becker, Limb-girdle, Fasioscapulohumeral muscular dystrophies and Myotonic Dystrophy type 2, while muscle fiber type I atrophy is most prevalent in DM1 [29].

1.2.3 Plasticity due to exercise
When muscles in healthy individuals are exercised, they respond according to type of exercise by hypertrophy of the muscle fibers, increased power and endurance, and to some degree, change of muscle fiber type. Inactivity reverses these effects [32, 33]. In patients with DM1, little is known regarding how exercise influences the muscles at the cellular level [34]. A recent Cochrane review concluded that there is not enough evidence to recommend type or degree of exercise to DM1 patients, except that moderate strength and endurance training do no harm [35]. However, a newly published DM1 mouse study demonstrates promising cellular effects after 7 weeks of running-wheel exercise with increased strength and endurance, more normalized EMG and reduced myotonia, increased number of mitochondria, and decreased cellular accumulation of toxic CUG RNA [36].

1.3 Myopathy in DM1
Muscle biopsy shows typical changes related to DM1 myopathy; fiber type 1 atrophy, fiber size variation and centrally located nucleus with chromatin clumps [11, 37]. The latter is a finding normally seen in constantly regenerating muscle fibers [37]. The levels of Creatine Kinase may be slightly elevated [2]. Recently, magnetic resonance imaging (MRI) has shown varying degrees of fat infiltration of affected muscles [38, 39].

1.4 Myotonia in DM1
Myotonia is a symptom of stiffness and delayed relaxation after contraction of the skeletal muscles. This phenomenon may lead to difficulties in motor functions involving the hand, chewing and swallowing. However, warming up with repeated contractions and warm
temperature may relax the muscle [2, 40]. The causes of myotonia in DM1 is thought to be hypersensitization of the cell membrane, caused by CIC-1 channel dysregulation [20].

**EMG** may show typical myopathy-related findings, with short duration of action potentials and increased recruitment of motor units. Typical for this disease is a discharge sound (myotonia), even in muscles where there is no obvious clinical myotonia. EMG may also be negative [2].

### 1.5 Muscles involved in DM1 adult forms

In DM1, clinical testing has shown decreased muscle strength and symmetrical involvement. In addition, the distal parts of the extremities are more affected than the proximal muscles of the limbs [3, 41]. The loss of muscle strength is related to CTG size and disease duration, as well as age at onset. The earliest and most severely affected muscles are reported to be the finger flexors, the dorsal flexors in the foot and the neck flexors [9]. Progression is slow. One study, using the MMT MRC 0-5, found a decline in muscle strength of - 0.11 units per year. Some patients will need walking aids, like a cane or frame, and a few will require a wheelchair [9]. A variety of activity and participation limitations may be present [42]. **Muscle MRI**, displaying a degree of fat infiltration, atrophy and edema, has shed light on the patterns of muscles affected. In the upper extremities, the flexor digitorum profundus, flexor pollicis longus and flexor digitorum superficialis muscles are the most affected [43]. In the lower extremities, the medial head of gastrocnemius and soleus muscles have the highest degree of fat infiltration [44].

In addition to muscles affected in the extremities, muscles affected in the face may be observed as ptosis and narrow temporal areas, and lead to the typical appearance of the myopathic face seen in DM1 patients, often accompanied by frontal balding. Affected orbicularis oculi and oropharyngeal muscles may respectively impair opening of the eyes and the ability to chew and swallow food, as well as impair speech [3, 45].

#### 1.5.1 Trunk muscles

The trunk is the part of the body without the extremities, the neck and the head. Trunk muscles are the muscles located around the vertebral column, the abdomen and pelvis [46]. These muscles flex, extend, rotate and laterally bend the trunk and spine. Their function is important for both postural stability and respiration [25, 27, 46].

Except from literature discussing and investigating pulmonary function, trunk muscles have previously been thought not to be impaired in DM1 [2, 9, 47, 48]. However, scoliosis is described,
but it is rare and occurs late in the progression of the disease [3]. In DM1, a disease specific motor impairment rating scale (MIRS) is developed to assess muscle involvement and progression of the disease. However, trunk muscle are not included in MIRS [41]. In a study of progression of muscle strength in DM1, trunk muscles were not included [9]. To the best of our knowledge, no studies investigating these muscles clinically have been published. Recently, a few MRI studies included abdominal and back muscles, and documented fat infiltration in both [38, 49, 50]. In 2017, after we started our study and published our first paper, Park et al. showed the abdominal rectus and back extensors at the lumbosacral level to be the most affected muscles in their MRI study [50].

1.6 Other organs and systems involved
Cataracts are frequently present and may be the only symptom in mildly affected patients. Cardiac disease is common. Arrhythmias and conduction disturbances may result in sudden death. Endocrine impairment of the thyroid, pancreas, hypothalamus and gonads may be present. Smooth muscle involvement may result in decreased peristalsis, and give symptoms of constipation [3, 45].

Symptoms of Central Nervous System (CNS) alterations are seen in both childhood and adult forms of DM1. Mental retardation occurs in childhood forms. In adult forms lower IQ, attention deficit, avoidant personality and low motivation have been described [51, 52]. Hormonal changes, sleep and respiratory disturbances in DM1 may also be symptoms of CNS affection. Abnormal MRI findings in both grey and white matter of the brain, correlating significantly to cognitive dysfunction, is observed [52, 53]. Autism is another CNS symptom which may be part of the disease in the congenital and childhood forms of DM1 [54]. Autism spectrum disorder (ASD) is a childhood-onset, neurodevelopmental disorder characterized by persistent deficits in social communication and interaction, as well as restricted, repetitive behavior and interests. The etiology of ASD is usually highly polygenic [55], but 15-20% have an identified rare genetic disorder that is the likely cause of the condition [56]. Difficulties with theory of mind and emotional participation are described in the adult DM1 group [53].

1.7 Fatigue and DM1
Fatigue, defined as an overwhelming sense of tiredness, lack of energy and exhaustion, is one of the most bothersome symptoms of DM1, and may be influenced by different factors [57]. Fatigue can be divided into experienced and physical, central or peripheral fatigue [58].
1.8 Pain and DM1

Pain can be acute or long-lasting and chronic, and may be caused by different mechanisms. The International Association of the study of Pain has defined pain as “An unpleasant sensory and emotional experience associated with, or resembling, actual or potential tissue damage” [59]. Pain experience has different qualities. It may be categorized as aching, deep, sharp, burning or a feeling of electric shock pain. Locations may be muscles and bones, and pain can be evoked by normal stimuli, like the light touch of a brush. Dependent on the quality of pain and location, pain may further be investigated and categorized as nociceptive or neuropathic [59, 60]. Nociceptive pain is defined as “pain that arises from actual or threatened damage to non-neural tissue, and is due to the activation of nociceptors”. In nociceptive pain, it is assumed that the nervous system is intact. Neuropathic pain is defined as “Pain caused by a lesion or disease of the somatosensory nervous system” [59]. The knowledge of pain in DM1 patients is limited. Studies investigating pain in mixed groups of neuromuscular diseases show high frequencies of chronic pain [61-66]. In a review, which included clinical symptoms of DM1 compared to Myotonic Dystrophy type 2, DM1 was considered as a diagnosis without pain [2].

1.9 Balance and Falls and DM1

Postural stability, or balance, is the ability to keep the body from falling, and within the base of support, e.g. the floor we stand and walk on, or the chair we sit in. To be in balance involves CNS integration of information from vestibular, visual and somatosensory systems. However, a prerequisite to be in balance is muscle strength to counteract the forces threatening balance. Both muscles in the extremities, as well as the trunk muscles, are involved in adjusting balance [25].

WHO defines falls as an event causing a person coming to rest inadvertently on the ground or floor or other lower level [67]. In DM1, falls are reported to be frequent and related to muscle strength in lower extremities [68]. In studies on falls in DM1, measurements of trunk muscle strength are not included [69-71]. DM1 patients report falling as one of their most bothersome symptoms [64].

1.10 Respiration and DM1

Respiration is the exchange of gas by different mechanisms acting together: air pressure and passive and active mobility. Mobility in the spine and ribcage allow the elasticity of the pleural membrane and lungs to increase and decrease the volumes of the lungs [72, 73]. Contraction of
the respiratory muscles are needed for normal ventilation. Primary inspiratory muscles at rest are the diaphragm and the intercostal muscles. Conversely, expiration is merely a passive process followed by relaxation of the diaphragm [73]. However, in deep respiration and in respiration related to activity, several muscles are involved. The scalenus, sternocleidomastoids and oblique externus muscles contribute to forced inspiration. On the other hand, the rectus abdominus, the oblique internus and the transvers abdomenus muscles contribute to forced expiration [27, 73], see figure 2. In addition, upper airway muscles are involved in both rest and exercise [74]. In DM1, myopathy in respiratory muscles may change respiratory values, and lead to a restrictive respiratory pattern [75]. Both weakening and myotonia of respiratory muscles are impairments which have been shown to influence respiration in DM1 [3, 48].

Figure 2. Respiratory muscles, with exception of the upper airway muscles

1.11 Treatment and guidelines for DM1

Currently, there is no known cure for DM1 [53]. However, multidisciplinary consensus-based guidelines of care on symptomatic treatment of systems and organs involved have been developed [76]. A Scandinavian consensus-based protocol for follow-up and treatment of DM1 symptoms, version 3, revised in 2010, is available online at the web site of the National Neuromuscular

---

1 This figure was published in Current Opinion of Physiology.10, Joseph Frank Welch, Shalaya Kipp and Andrew William Sheel, Respiratory muscles during exercise: mechanics, energetics and fatigue, 102-109, Copyright Elsevier 2019.
1.12 Clinical challenges leading up to this thesis

At Drammen Hospital Vestre Viken Hospital Trust (DH VV-HT), DM1 patients have been followed in a multidisciplinary outpatient clinic for many years. The Scandinavian protocol for DM1 is an important guideline in this work. However, some of the clinical phenomena we observed were not explicitly described as part of this diagnosis, and they were absent in both follow-up programs and scientific literature. In particular, this was the case for trunk (abdominal and back muscles) muscle weakness and pain. These observations were contradictory to the descriptions of DM1 as a painless myopathy with distal to proximal progression of muscle affection in the extremities. Trunk muscles were only mentioned anecdotally and only late in the progression of the disease [3]. In addition, the widely used DM1 disease specific muscle impairment rating scale MIRS, does not include testing of trunk muscles [41]. Pain had also not been described as an important part of DM1 [2, 3].

2. Thesis Aims

2.1 Main aims

To investigate the presence of trunk muscle impairment, myopathy and pain in adult patients with DM1.

2.1.1 Aims of study I

Aims in study I were to detect whether, and to what extent, trunk muscle groups were impaired in DM1 patients, and to investigate the progression of muscular impairment in these patients by relating muscle strength to disease duration. Furthermore, we wanted to examine whether strength in the various muscle groups correlated with CTG size, disease duration and walking capacity, mobility and balance as measured by the six-minute walk test (6MWT), Rivermead mobility index (RMI) and Timed up and go (TUG).

2.1.2 Aims of study II
Aims in study II were to investigate muscle size (diameter and area) and fat infiltration in trunk muscles in DM1 patients, and compare the results to an age and gender matched control group. In the DM1 patients, we also aimed to explore whether the amount of fat and the size of the trunk muscles correlated with trunk muscle strength, respiratory function and other motor measurements.

2.1.3 Aims in study III
Aims in study III were to investigate gender differences regarding intensity and location of pain, and to ascertain whether the degree of CTG expansion, disease duration, motor and psychological function were related to pain.

2.1.4 Aims of study IV
Aims in study IV were to investigate the presence of neuropathic pain and small and large fiber neuropathy in the adult form of DM1, and to explore whether neuropathy was related to CTG size, disease duration and other clinical DM1 symptoms. We further investigated if small fiber findings on skin biopsy were different in the DM1 group compared to reference values from healthy controls.

3. Materials and methods

3.1 Design, participants and inclusion
Patients were recruited through the Department of Neurology, Rheumatology and Rehabilitation at DH VV-HT and the Department of Neurology, Oslo University Hospital (OUH), as well as through the Norwegian society of muscle disease’s (FFM) magazine” Muskelnytt”, and the National register of inherited neuromuscular diseases.

This is an observational study. Study one, three, and four are cross sectional, while the second study has a case-control design. Numbers of patients included in the four studies were influenced by the general prevalence of DM1, which is a rare disorder. In addition, numbers of patients included were based on published abstracts from preliminary data on 12 patients (study I), previous literature of studies on neuropathy in DM1 (study IV), and calculated power (study II, and III) to answer the different study questions and hypothesis. Some of the research questions were explorative.
General inclusion criteria were a genetically verified DM1 diagnosis and adult age. The general exclusion criteria were congenital and childhood forms of DM1, due to their different clinical presentation [77] compared to adult forms. In total, 55 patients with a verified diagnosis and a typical history of DM1 adult form were invited. Of these, 50 patients accepted the invitation. The subjects who declined to participate informed us they were either too sick (one) or too healthy (one), while three were too busy.

In 2012-2017 the numbers of inhabitants in Buskerud county was respectively 265 164 - 279 714 persons (www.bfk.no dated 23.2.2018). During this period, we included 27 DM1 patients from Buskerud, which is about 9.9/100 000.

3.1.1 Inclusion to the separate studies

Participants Paper I
In paper I, the general inclusion and exclusion criteria applied. All patients referred to the inclusion site at the Department of Neurology, Rheumatology and Rehabilitation at DH VV-HT between 2012 and 2014 were informed about and invited to participate in the study. Patients from other counties in the south-east part of Norway (Oslo, Oppland and Telemark) were also informed and invited. Those who responded to the invitation were successively included. Two patients (5%) of 40 invited declined to participate. Thirty-eight genetically confirmed DM1 patients were recruited, 21 men and 17 women. Thirty-five participants were walking independently, two needed a walking aid (walking frame), and one needed a wheelchair. All patients included at DH VV-HT were examined by local professionals, these were neurologists, psychologists, a socionom, and a physiotherapist (the PhD candidate).

Participants Paper II
Participants in the MRI study were included during 2016-2017. The general inclusion and exclusion criteria applied. In addition, patients with contraindications to MRI, like metal implants and pacemakers, were excluded. Furthermore, some (n=12) subjects were not included because they lived too far away from DH VV-HT, where the MRIs were performed. Subjects that were not able to lie down for 12 minutes, as well as hold their breath for 10 seconds, were excluded. Sixteen of the participants from the first study (n=38) were invited and included in the MRI study. In addition, five new participants from the south-east part of Norway (Viken, Vestfold, and Akershus county) were included. One person declined to participate, and reported no reason for this. Thus, 96% responded positively to study II. All participants in the MRI study were able to walk independently. In addition, 20 healthy age and gender-matched controls were recruited.
through a written announcement to employees at the hospital. The invitation to participate was not restricted to employees. Participants were included consecutively as they returned written consents. All patients were examined by local professionals at DH VV-HT. These were one neurologist and one physiotherapist (the PhD candidate) as well as radiographs performing the MRIs. In addition, one radiologist from DH and one radiologist and radiographer from OUH participated.

Participants Paper III
The third study included all 50 patients participating in this PhD study, and the general inclusion and exclusion criteria applied. The inclusion period was from 2012 to 2017. For characteristics, see table 2. Main inclusion site was DH VV-HT, and local professionals examined the patients (neurologists, psychologists, socionom and the PhD candidate). In addition, seven patients were included at the University Hospital of Northern Norway (UNN). At UNN, one local neurologist and one local psychologist examined the patients. In addition, one neurologist from OUH and the PhD candidate participated in this work.

Participants Paper IV
In the fourth study, inclusion sites were UNN and OUH and DH VV-HF. The general inclusion and exclusion criteria applied. In addition, the most severely impaired and fatigued patients who needed support from another person to be able to travel to the investigation site, were excluded. Thirty-two patients living in the proximity to the hospitals were invited. Twenty patients (62 %) of those invited, accepted the invitation, and were included between June 2016 and September 2017. One neurologist and one psychologist from UNN, one neurologist from OUH and the PhD candidate performed the examinations. Analysis of the skin biopsies were done at UNN. All patients included at DH VV-HT were examined by local professionals (neurologist, psychologist, the PhD candidate).

For timeline of the different studies see figure 3.
Figure 3. Timeline of inclusions in the different studies and publication of the papers

![Timeline of inclusions in the different studies and publication of the papers](image)

Table 2. Characteristics of the 50 participating DM1 patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N50</th>
<th>Men 24</th>
<th>Women 26</th>
<th>Difference between men and women p/Cohens d</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean, SD, (Range)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>40.12, SD: 12.6. (19-63)</td>
<td>37, SD: 13.8 (19-63)</td>
<td>43, SD: 10.7 (23 - 62)</td>
<td>ns</td>
</tr>
<tr>
<td>CTG kb</td>
<td>1.8, SD: 1.4 (0.230-5.4)</td>
<td>1.3 SD: 1.1 (0.270 - 4.7)</td>
<td>2.3 SD: 1.5 (0.230 – 5.4)</td>
<td>p=0.007/0.82</td>
</tr>
<tr>
<td>Disease duration, years</td>
<td>19.12, SD: 10 (5-42)</td>
<td>16.4 SD: 9.6 (5-42)</td>
<td>21.5 SD: 9.7 (6-40)</td>
<td>ns</td>
</tr>
<tr>
<td>Mean strength of trunk muscles (MTT 0-3)</td>
<td>1.7, SD: 0.5 (1-2.6)</td>
<td>1.8, SD: 0.5 (1-2.6)</td>
<td>1.6, SD: 0.4 (1-2.3)</td>
<td>ns</td>
</tr>
<tr>
<td>Mean strength of distal extremity muscles (MTT 0-3)</td>
<td>2.3, SD: 0.5 (1.5-3)</td>
<td>2.3, SD: 0.5 (1.5-3)</td>
<td>2.3, SD: 0.5 (1.5-3)</td>
<td>ns</td>
</tr>
<tr>
<td>Mean strength of proximal extremity muscles (MTT 0-3)</td>
<td>2.6, SD: 0.3 (2-3)</td>
<td>2.7, SD: 0.3 (2-3)</td>
<td>2.6, SD: 0.3 (2-3)</td>
<td>ns</td>
</tr>
</tbody>
</table>

Mean, SD, (min/max) are presented. Exact p levels are given for differences < 0.05 between men and women and the Cohens d effect size is reported. (DM1: Myotonic Dystrophy type 1, CTG: Cytosine, Thymine, Guanine, MMT: Manual Muscle strength test.)
Five patients could not walk for longer distances and used a wheelchair. Persons with MRC <grade 2 for ankle dorsal flexion used an ankle orthosis preventing drop foot.

29 participants were categorized to MIRS score 1-3 (mild to moderate), and 21 participants to MIRS score 4-5 (severe).

Two participants belonged to the late adult DM1 form and 48 to the classic DM1 form. If categorizing to juvenile form 28 of the participants belonged to this DM1 form.

For characteristics of the participants in the different papers see table 3.

Table 3. Characteristics of the participants in the different studies

<table>
<thead>
<tr>
<th></th>
<th>Study I n=38</th>
<th>Study II n=20/20</th>
<th>Study III n=50</th>
<th>Study IV n=20</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td></td>
<td>range</td>
<td>range</td>
<td>range</td>
<td>range</td>
</tr>
<tr>
<td>Age: years</td>
<td>39 (12.4)</td>
<td>39 (12.8)</td>
<td>40.1 (12.6)</td>
<td>38.8 (12.8)</td>
</tr>
<tr>
<td></td>
<td>20-63</td>
<td>19-62</td>
<td>19-63</td>
<td>19-62</td>
</tr>
<tr>
<td>CTG kb</td>
<td>1.75 (1.39)</td>
<td>1.4 (0.8)</td>
<td>1.8 (1.4)</td>
<td>1.8 (1.3)</td>
</tr>
<tr>
<td></td>
<td>0.23-5.4</td>
<td>0.3-3.1</td>
<td>0.23-5.4</td>
<td>0.27-4.5</td>
</tr>
<tr>
<td>Sex</td>
<td>female</td>
<td>female</td>
<td>female</td>
<td>female</td>
</tr>
<tr>
<td></td>
<td>17</td>
<td>12</td>
<td>26</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>male</td>
<td>male</td>
<td>male</td>
<td>male</td>
</tr>
<tr>
<td></td>
<td>21</td>
<td>8</td>
<td>24</td>
<td>7</td>
</tr>
<tr>
<td>Form of DM1</td>
<td>mild adult</td>
<td>mild adult</td>
<td>mild adult</td>
<td>mild adult</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>classic</td>
<td>classic</td>
<td>classic</td>
<td>classic</td>
</tr>
<tr>
<td></td>
<td>36</td>
<td>20</td>
<td>48</td>
<td>19</td>
</tr>
<tr>
<td>MIRS grade</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>7</td>
<td>15</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>4</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>7</td>
<td>17</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>0</td>
<td>4</td>
<td>1</td>
</tr>
</tbody>
</table>

3.2 Cooperation

DM1 is a rare disease and cooperation between different hospitals was necessary to be able to include the number of patients needed. The study was initiated at the section of Habilitation,
department of Neurology Rheumatology and Rehabilitation DH VV-HT, where inclusion of participants was done in the interdisciplinary follow-up outpatient DM1 clinics. In addition, the Department of Neurology, OUH and the section of Clinical Neurophysiology, UNN participated and included patients. The department of Diagnostic Imaging at DH VV-HF performed and analyzed the MRIs, the Division of Radiology and Nuclear Medicine at OUH analyzed the MRIs and the Department of Medical Genetics, Haukeland University Hospital reassessed the CTG repeats. The Neurology Research Laboratory, at the Arctic University of Norway Tromsø, analyzed the skin biopsies.

3.3 Measures
This study was performed with a broad set of measures, including clinical examination, questionnaires assessing motor and psychological function, blood samples for new genetic testing, muscle MRIs, pain reports, neurophysiological investigations, skin biopsies and information from the patients’ medical files.

3.3.1 Motor function measures and questionnaires
Skeletal muscle strength: Muscle strength was assessed with the MRC 0-5 scale for MMT [26]. MMT is a widely accepted method, also in studies investigating progression of muscle strength in DM1 patients [78, 79]. It has been validated and is reliable in DM1 populations [41, 80]. However, the MRC scale has been criticized for its unequal categorical width (score 1 and 2 too narrow and 4 to wide), for providing solely ordinal data, and for its low discrimination between categories when used in clinical practice [81]. To counteract these limitations in the present study, the MRC 0-5 scale was recoded to a modified 0-3 scale, according to Vanhoutte et al. [81]. By Rasch modelling of strength measure data from 1065 patients with different neuromuscular disorders, including DM1, Vanhoutte et al. documented an improved ability to discriminate between the strength categories when using the modified 0-3 scale. This method restored thresholds, enabling MMT to be analyzed as an interval scale (see Table 4) [81].

In general, muscle strength testing is interpreted by the tester, and pain, joint mobility, compensation and motivation must be controlled for according to standardized methods [27]. For demonstrations of trunk muscle strength tests see figure 4.
**Table 4. Medical Research Council; recoding from six-point to modified 0-3 scale**

<table>
<thead>
<tr>
<th>Six-point ordinal scale</th>
<th>0-3 interval scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 = No muscle contraction</td>
<td>0 = Paralysis</td>
</tr>
<tr>
<td>1 = Flicker or trace of muscle contraction</td>
<td>1 = Severe weakness defined as &gt;50% loss of strength</td>
</tr>
<tr>
<td>2 = Active movement with gravity eliminated</td>
<td>2 = Slight weakness &lt;50% loss of strength</td>
</tr>
<tr>
<td>3 = Reduced power but active movement against gravity</td>
<td>3 = Normal strength</td>
</tr>
<tr>
<td>4 = Reduced power but active movement against gravity and resistance</td>
<td></td>
</tr>
<tr>
<td>5 = Normal power against full resistance</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 4. Demonstration of back and abdominal muscle strength tests**

Validating back muscle strength test: Observing passive mobility of back extension

Performing the back-extension muscle strength test, here measuring score 2 (MRC 0-3): active movement against gravity throughout the full range of motion, with the arms along the side of the body. Fixation should be applied above the knees as indicated by the arrow, or at the pelvic.
Performing the curl up, an abdominal muscle strength test: here measuring score 2 (MRC 0-3), active movement against gravity through full range of motion, arms positioned along/ in front of the body. Fixation should be applied above the ankles, as indicated by the arrow and, if needed at the head/neck for DM1 patients with scores below 2 in neck flexor muscles.

The disease specific Muscular Impairment Rating Scale (MIRS) [41] was used to investigate the severity of muscular impairment. MIRS is a 5-point scale where 1 is no muscular impairment, 2 is minimal signs (myopathy in face and neck muscles), 3 is distal weakness (involvement of distal extremities), 4 is proximal weakness (involvement of proximal extremities) and 5 is severe proximal weakness (of muscles in extremities). The MIRS is valid and reliable. However, Mathieu et al. state that caution must be exercised when interpreting small samples sizes due to low interrater reliability [41].

The six-minute walk test (6MWT) was used for measuring walking capacity. It was conducted according to the guidelines of the American thoracic society [82], apart from the corridor track in the present study being 20 meter instead of 30 [83]. The 6MWT is found feasible and reliable as a measure of walking capacity in DM1 patients [84].

Timed Up & Go (TUG) [85] expressed in seconds was used for evaluating mobility and balance [25]. The time used to get up from a chair with an armrest (0.45 m high/normal chair), walk three meters, turn, walk back and sit down, was recorded. The patients were instructed to walk in a safe manner and as fast as possible. The procedure was done twice, and the second test was recorded. Acceptable test-retest stability has been documented in DM1 patients [85, 86].
Different approaches can be used to examine balance. One tests for static (standing or sitting positions on a stable base of support) or dynamic balance (while moving the body or base of support). Others evaluate the change of balance with eyes closed or open, or with external perturbations [25]. In this study, we investigated dynamic balance by using the TUG.

Rivermead Mobility Index (RMI) is a questionnaire that measures general mobility [87]. RMI consists of 15 items. The sum range is 0-15. A high sum indicates better mobility performance. The questions range from whether the person is able to independently turn from the back on to their side, to sit up, sit unsupported and to run or walk 10 meters, fast, in 4 seconds. One question, assessing whether the person is able to stand unsupported for 10 seconds, requires observation. RMI is reliable and valid in other populations with different neurological conditions [87, 88]. It was also used in a DM1 study of function and disability [42], and is a recommended outcome measure for DM1 patients [89].

The Katz Index of Independence in Activities of Daily Living (Katz ADL) [90, 91] is a questionnaire evaluating personal activities of daily life (P-ADL) in adults and the elderly. The Katz is reliable and valid, and it has been used in a previous DM1 study [42, 92, 93].

Fatigue severity scale (FSS) was used to measure general fatigue [94]. The FSS was developed by Krupp et al. to determine the impact of fatigue on daily life in multiple sclerosis and systemic lupus erythematosus [95]. Later, it has also been used to determine fatigue in neuromuscular disorders, [96, 97] and has been found to be reliable in DM1 patients [98].

Hight and weight was measured, and Body Mass Index (BMI) [99] was calculated for all persons included, both cases and controls.

3.3.2 Information from medical files

Information on the need for bi-level positive airway pressure (BiPAP), and the respiration measure forced vital capacity (FVC) [100] was collected from the patients’ medical files. The FVC closest to time of inclusion was used, and all were performed within 3 years. We also recorded any diagnosis of diabetes or thyroid dysfunction from the patients’ medical records. In addition, other neurological conditions or diagnoses of importance for motor function and pain, such as stroke, MS, Parkinson, entrapment or sciatica, were recorded.
3.3.3 MRI measurements

MRI was completed in 20 DM1 patients and 20 controls. MR imaging of the trunk muscles, from the 11th thoracic vertebra level to the level of the lesser trochanter of the hip, were examined using 1.5 Tesla. Total scanning time was approximately 15 minutes.

The following muscles were scored: the rectus abdominis -, the abdominal oblique -, the abdominal transverse -, the erector spinae -, the iliopsoas - and the gluteus maximus.

Muscle fat infiltration and muscle size were assessed.

Fat infiltration was scored according to the Mercuri score [101], see table 5. The Mercuri score was developed for use in muscular dystrophy, and is widely used when reporting muscle fat infiltration in myopathic muscles[102, 103].

<table>
<thead>
<tr>
<th>Mercuri score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No fat infiltration</td>
</tr>
<tr>
<td>1</td>
<td>Fatty streaks</td>
</tr>
<tr>
<td>2</td>
<td>&lt; 30% fat infiltration</td>
</tr>
<tr>
<td>3</td>
<td>&gt; 30% but &lt; 60% fat infiltration</td>
</tr>
<tr>
<td>4</td>
<td>&gt; 60% fat infiltration</td>
</tr>
<tr>
<td>5</td>
<td>Totally replaced by fat</td>
</tr>
</tbody>
</table>

Mercuri score 0 and 1 were defined as normal. The rectus abdominis muscles were scored in two intervals, above and below the umbilicus. The erector spinae muscles (including deep layers of paraspinal muscles) were scored in three intervals (above the L2/L3 disc level; between the L2/L3 and the L4/L5 disc level; and below the L4/L5 disc level).

The maximal thicknesses (mm) of the rectus abdominis muscles, the external and the internal abdominal oblique muscles and the abdominal transverse muscles were registered. The muscles were scored at a level above the umbilicus. The maximal thicknesses of the rectus abdominis muscles were also registered at a level below the umbilicus.

The areas (mm²) of the erector spinae muscles were registered in the L1/L2, L3/L4 and L5/S1 disc levels [104]. The areas (mm²) of the Psoas muscles were registered in the L4/L5 disc
level. The areas of the gluteus maximus muscles were not analyzed. All muscle sizes were assessed, including the areas with fatty degeneration. Muscle edema, was assessed at preselected standardized levels that were identified with the Tesla1 weighted images. For further details regarding the MRI procedures see paper II.

The MRI scans were scored independently by two radiologists, with 20 years of experience within the musculoskeletal field. They were aware of age and gender but blinded for clinical information. The images were anonymized and scored in a random order. The readers were blinded for each other’s scoring and whether the images belonged to patients or controls. Interrater variability between the two radiologists reading the MRIs was calculated by interclass correlation (ICC (3.1) two - way mixed, consistency). Mean ICC was 0.90 (excellent).

3.3.4 Cognitive measures and psychological questionnaires

General cognitive function measured by Intelligence Quotient (IQ) was assessed with the Wechsler Adult Intelligence Scale (WAIS IV) [105]. Screening tools for psychiatric problems were used to get a numeric estimate of the degree of the problems. Anxiety and depressive symptoms were assessed using Beck’s Anxiety Inventory (BAI) [106] and Beck’s Depression Inventory (BDI) [107]. BDI has previously been used in DM1 studies [108, 109]. The Autism Spectrum Quotient (AQ) [110] was used for assessing the amount of ASD symptoms. The AQ is one of the few existing ASD screening tools that is based on self-report. The AQ is not suitable for diagnostic purposes, but it has been shown to meaningfully differentiate groups with low levels of ASD traits [111]. For BAI, BDI and AQ, a higher score represents more symptoms. For quality of life, the WHO quality of life - bref (WHO QoL-BREF) questionnaire was used [112]. For WHO QoL, a higher score represents higher reported quality of life.

All questioners were completed by the patients in the clinic with an experienced clinician present.

3.3.5 Pain measures

Patients were instructed to mark and score intensity of chronic pain, defined as pain that had been present for at least 3 months. Pain locations were investigated by pain drawings, and the
number of pain sites was summarized from these drawings [113]. Headache was excluded. Pain intensity was scored by the subjects as the experienced mean pain intensity, and was based on the numeric rating scale (NRS 0-10): no pain=0, mild pain= 1-3, moderate pain= 4-6, severe pain=7-10 [114].

3.3.6 Neuropathy measurements

The 20 patients included were asked about the presence of pain and its quality. When subjective symptoms indicating neuropathic pain, which are pain qualities like sharp, burning and electric shock, are present together with clinical and objective findings of neuropathy, neuropathy as the cause of pain is probable. The probability increases with more objective findings [60, 115].

Large and small fibers were investigated with neurography, quantitative sensory testing of thermal thresholds, and skin biopsy for quantification of Intraepidermal nerve fiber density (IENFD). Neurography was performed on Keypoint Classic® and Keypoint G4® machines. Nerve conduction velocities, amplitudes and distal latencies of the median and ulnar (motor and sensory) nerves in one upper extremity were examined. In the lower extremities, the motor nerve conduction velocities, amplitudes and distal latencies of the peroneal and tibial nerves, as well as the sensory sural, medial plantar and peroneal superficial nerves, were examined in both legs. The neurography results were compared with normal values supplied by the manufacturer. In this study, we regarded three pathological nerves in the lower extremities, including at least one sensory nerve, as compatible with large fiber neuropathy. Heat detection thresholds, cold detection thresholds, heat pain detection thresholds and cold pain detection thresholds were determined using a computerized Thermotest® (Somedic AB, Sweden), as described elsewhere [116]. Heat detection thresholds and cold detection thresholds were calculated as the average of five consecutive temperature recordings. These thresholds were determined at the thenar eminence of the left hand, at the lateral aspect of the left thigh (approximately 20 cm above knee level), at the lateral aspect of the left leg (approximately 15 cm below knee level), and at the dorsum of the left foot. Heat pain detection thresholds was determined at the dorsum of the foot, and calculated as the average of three recordings at 10-second intervals. Thresholds were compared to normal material obtained by Ørstavik et al. [117]. Findings of increased thresholds for cold detection thresholds, heat detection thresholds, or both, at the dorsum of the foot, indicated small fiber neuropathy.
Two skin biopsies were obtained from the distal part of the leg, 5-10 cm above the lateral malleolus, with a 3-mm disposable circular needle, under local anesthetic. Fifty-micron freezing sections were immunostained with the panaxonal marker PGP 9.5. The number of separate intraepidermal nerve fibers in three sections from each biopsy was counted, and the total length of epidermis was measured. IENFD in patients was compared with data from 106 healthy adult individuals analyzed in the same laboratory [118].

For which measures used in the different papers see table 6

Table 6. Measurements in the different papers

<table>
<thead>
<tr>
<th>ALL PARTICIPANTS</th>
<th>Paper I</th>
<th>Paper II</th>
<th>Paper III</th>
<th>Paper IV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at diagnosis, onset symptoms: Clinical history</td>
<td>•</td>
<td>•</td>
<td>•</td>
<td>•</td>
</tr>
<tr>
<td>Neurological status: examination</td>
<td>•</td>
<td>•</td>
<td>•</td>
<td>•</td>
</tr>
<tr>
<td>Genetic Testing: Southern blot analyses of CTG repeats</td>
<td>•</td>
<td>•</td>
<td>•</td>
<td>•</td>
</tr>
<tr>
<td><strong>Motor function</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manual Muscle strength test: MMT</td>
<td>•</td>
<td>•</td>
<td>•</td>
<td>•</td>
</tr>
<tr>
<td>Walking capacity: 6MWT</td>
<td>•</td>
<td>•</td>
<td>•</td>
<td></td>
</tr>
<tr>
<td>Functional Balance: TUG</td>
<td>•</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General mobility: RMI</td>
<td>•</td>
<td>•</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Self-care: Katz ADL Questionnaire</td>
<td></td>
<td></td>
<td></td>
<td>•</td>
</tr>
<tr>
<td><strong>Pain QOL and fatigue</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quality of life: WHOQOL BREF</td>
<td></td>
<td></td>
<td></td>
<td>•</td>
</tr>
<tr>
<td>Pain: NRS and pain drawing</td>
<td>•</td>
<td></td>
<td>•</td>
<td>•</td>
</tr>
<tr>
<td>Fatigue: FSS questionnaire</td>
<td>•</td>
<td></td>
<td></td>
<td>•</td>
</tr>
<tr>
<td><strong>Psychological factors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Social-cognitive function: Autism Quotient (AQ)</td>
<td>•</td>
<td></td>
<td></td>
<td>•</td>
</tr>
<tr>
<td>Depression, Anxiety: Beck’s Inventory</td>
<td>•</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cognitive assessment: Wechsler IQ test</td>
<td>•</td>
<td>•</td>
<td>•</td>
<td>•</td>
</tr>
<tr>
<td><strong>Other somatic measures</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes, Thyroid dysfunction: from medical records</td>
<td>•</td>
<td></td>
<td>•</td>
<td>•</td>
</tr>
<tr>
<td>Respiratory function: BiPAP and FVC: from medical files</td>
<td>•</td>
<td>•</td>
<td></td>
<td>•</td>
</tr>
<tr>
<td>BMI: examination</td>
<td>•</td>
<td>•</td>
<td></td>
<td>•</td>
</tr>
</tbody>
</table>
Neurophysiological tests

Large fibers: Neurography
Small fibers: Thermal thresholds

Histopathological test

Small fibers: Skin biopsy

Imaging

MRI of trunk muscles

3.4 Analysis

We used the statistical package IBM SPSS statistics for windows, version 21.0 (paper I), 24.0 (paper II and III), and 25.0 (paper IV) in analyzing the data. Descriptive data are reported as percentage, central tendencies (mean and median), variation (SD) and range. Further analyses were correlations, and group differences. Parametric statistics was used for continuous and normal distributed variables. Non-continuous and non-normal distributed variables were analyzed by nonparametric statistics. In two of the papers (II and III) linear regression was used to control for confounding. The assumptions (linear relationship between outcome and independent variables, multivariate normality, homoscedasticity and multi collinearity) for linear regression were met. See table 7, for which analysis were used in the different papers. Statistical significance was set at p≤0.05. To control for multiple comparisons Bonferroni corrections were done in paper II, and significant p level set to ≤0.005 when for analysis case-control differences regarding muscle size and muscle fat infiltration in the individual muscles. Bonferroni correction was also done when testing for gender differences regarding number of pain locations and pain intensity in paper III, significant p level was set to ≤ 0.01. Corrections of p levels were not done for descriptive and explorative analysis. Cohens d was used to calculate effect sizes and Cohens d between 0.2-<0.5=small, between 0.5-<0.8=medium and >0.8=large.

Table 7. Statistical analysis in the different papers

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Paper I</th>
<th>Paper II</th>
<th>Paper III</th>
<th>Paper IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Descriptive</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency</td>
<td>•</td>
<td>•</td>
<td>•</td>
<td>•</td>
</tr>
<tr>
<td>Mean, SD, Range</td>
<td>•</td>
<td>•</td>
<td>•</td>
<td>•</td>
</tr>
<tr>
<td>Median</td>
<td>•</td>
<td>•</td>
<td>•</td>
<td>•</td>
</tr>
</tbody>
</table>
**Exact test**  
**Correlations**  
- Pearson’s r  
- Spearman’s rho  
**Group tests**  
- Independent sample t test.  
- Mann-Whitney U test.  
- Wilcoxon signed rank test.  
- Cohens d test  
**Regression**  
- Linear forced entry  
**Reliability**  
- Cronbach’s alpha  
- Inter Class Correlation  
3.1 two way mixed

4. Results

4.1 Summary of papers

The aim of the first study was to investigate whether trunk muscle strength was impaired in adult DM1 patients. Furthermore, we sought to ascertain whether such impairment was correlated with the CTG size, disease duration, walking capacity, general mobility and balance. We also explored whether patients with impaired trunk muscle strength had respiratory affection. Thirty-eight genetically verified, adult DM1 patients from the south-east region of Norway were included at DH VV-HT. We assessed muscle strength in the muscles of the neck, abdomen, back and extremities by the MMT. Walking capacity was measured by the 6MWT, general mobility was measured by the RMI, and dynamic balance was investigated by the TUG. The number of CTG repeats was reassessed at the time of inclusion by Southern blot analysis, and we noted time, in years, since the first symptom of DM1, as reported by the patients. Analysis of the data revealed severe and relatively early impairment of the trunk muscles. Trunk muscle strength was significantly correlated with CTG repeats ($r=-0.64$, $p<0.001$), walking capacity ($r=0.67$, $p<0.001$), general mobility ($r=0.66$, $p<0.001$) and balance ($r=-0.58$, $p<0.001$). We also found that patients with the need for respiratory aid (BiPAP) had markedly impaired muscle strength of the abdominal and back muscles (9 out of 38). BMI and gender
were considered possible confounders, but neither were related to any strength measures. We concluded that trunk muscle impairment in adult DM1 patients may be early and severe. This could have consequences for everyday functioning, and may account for possible injuries and increased risk of falls.

Based on our findings in the first study, we wanted to investigate further which, and how, trunk muscles were affected. We used MRI and measured the degree of fat infiltration and muscle size, with a case-control design. We hypothesized that there was a case-control difference for MRI findings in adult DM1 patients, compared to healthy controls, matched for age and gender. We also investigated the presence of edema in both groups. Furthermore, we explored correlations between the two MRI measures using CTG size and disease duration, muscle strength (MMT) in the abdominals and the back extensors, walking capacity (6MWT), general mobility (RMI), balance (TUG) and respiratory function measured by forced vital capacity (FVC), in the DM1 group. Results showed significant case-control differences for sum scores of muscle fat infiltration in the abdominals \( (p=0.001) \) and in the back muscles \( (p<0.001) \), as well as for muscle size in the abdominals \( (p=0.002) \) and back muscles \( (p=0.030) \). The DM1 group had more fat infiltration and smaller muscle size compared to the control group. Some of the muscles were more affected than others. The psoas muscle was within normal range, while the cranial part of the rectus abdominus and the lowest part of the erector spinae muscle were the most severely affected, with \( \geq 40\% \) of the patients showing \( >30\% \) fat infiltration, and \( 10\% \) of the patients showing \( >60\% \) fat infiltration and \( 5\% \) total fat replacement in these muscles. Edema was present to a larger extent in DM1 patients compared to controls (nine subjects versus one). Significant correlations were present between fat infiltration in the abdominals and back-extension strength \( (\text{rho}= -0.52, p=0.018) \), and between muscle size and strength in the abdominals \( (r=0.47, p=0.035) \). Fat infiltration in the abdominals were significantly correlated with lower scores of the RMI \( (\text{rho}= -0.63, p=0.003) \), higher scores of the TUG \( (\text{rho}= 0.63, p<0.003) \) and reduced FVC \( (\text{rho}= -0.49, p=0.040) \). Muscle size in the abdominals was correlated with FVC \( (\text{rho}= 0.55, p=0.018) \). Disease duration was correlated with fat infiltration in the abdominal muscles \( (\text{rho}= 0.47, p=0.037) \). Gender differences regarding the MRI measure of muscle size was different between cases and controls. In the DM1 group, there was less difference in muscle size between men and women in the back muscles, and larger differences in the abdominals, than in the control group. However, all the differences were significant, and men had larger muscles than women. In conclusion, findings in the second study confirmed a difference in fat
infiltration and atrophy in abdominal and back muscles between DM1 patients and healthy age and gender-matched controls. In DM1 patients, fat infiltration was associated with reduced muscle strength, mobility, balance and lung function, while muscle size was associated with muscle strength and lung function.

The MRI results show myopathy in both abdominal and back muscles, which confirms the trunk muscle impairments observed in paper one. See figure 5 for demonstration of MRI findings in case and control.

*Figure 5. MRIs of case, and control*

MRI of case showing fat infiltration Mercuri score 3 (>30%) in the cranial abdominal rectus (open arrow head) and external oblique muscles (arrow head), and Mercuri score 2 (<30%) in the caudal abdominal rectus (arrow) and erector spinae (*) muscles.

MRI of control showing Mercuri score 0 and 1 (fatty streaks).

We have frequently seen patients with trunk muscle impairment and pain in the DMI outpatient clinic. The aim of the third study was to investigate pain in DM1, and whether CTG size, disease duration, BMI and motor-and psychological function were related to pain. We also aimed to explore whether trunk muscle impairment was related to pain. We hypothesized that there were gender differences regarding intensity and location of pain, and
we explored associations to other DM1 symptoms in men and women. Pain was investigated in 50 adult DM1 patients by combining clinical assessments and self-reporting of pain intensity and location. Pain results were related to CTG size, disease duration, muscle strength in trunk and extremities, walking capacity (6MWT), personal activity of daily life (KATZ P-ADL), BMI and respiration measured by forced vital capacity (FVC). In addition, the degree of reported pain was related to the quality of life measured by WHOQOL-BREF, fatigue measured by FSS and psychological functions measured by BDI, BAI, IQ and AQ. Pain was reported in 84% of the patients, it was widespread and symmetrical. The most frequent locations were the lower back, the neck and the palmar side of the hands. Furthermore, pain was significantly correlated with CTG size ($r=0.29 \ p=0.050$), disease duration ($r=0.38 \ p=0.007$), quality of life ($r=-0.37 \ p=0.009$), fatigue ($r=0.33 \ p=0.02$) and FVC ($r=-0.51, p=0.005$). We found significant gender differences for pain intensity (asymptotic $p=0.001$) and the number of pain locations (asymptotic $p=0.01$), with higher scores for females. In male subjects, the number of pain locations was correlated with quality of life and with the autism quotient. In females, pain intensity was correlated with activity, respiratory function and BMI. Pain in DM1 was prevalent, with a strong association to lung functioning. Significant gender differences were present for pain intensity and the number of pain locations. Gender also influenced how pain was correlated with other DM1 symptoms and findings. Our results highlight the importance of pain assessment in DM1 patients, and to account for gender differences.

The aim of the fourth paper was to further investigate our previous findings of high prevalence of pain in adult DM1 patients. We specifically wanted to explore whether the pain experienced by the patients could be related to small or large fiber neuropathy. We also explored whether neuropathy was related to CTG size, disease duration, and other clinical DM1 symptoms (muscle strength, fatigue). Twenty patients were included. Assessments of pain descriptions, neurological examination and objective examination of the peripheral nerve system by quantitative sensory testing, skin biopsies and neurography were conducted. Statistical analysis for group differences and frequencies were performed. Six patients (30%) out of 20 patients with DM1 described symptoms more typical for neuropathic pain. Three of these had objective findings of small or large fiber neuropathy, as well as clinical sensory findings. Together, large and/or small fiber neuropathy was present in 50% of the patients with DM1. The intra-epidermal nerve fiber density was significantly lower ($p<0.001$, Cohen’s d =1.2) in the 20 patients with DM1 (mean 8.16, SD: 2.28) compared to a reference
group (N =106, mean 12.43, SD: 4.59). Patients with large fiber neuropathy had significantly lower muscle strength (p=0.009) than patients without large fiber neuropathy. Finally, fatigue was associated to neuropathic pain (p=0.020). In conclusion, symptoms and findings of neuropathic pain seems more frequent in patients with DM1 compared to the general population. IENFD was significantly lower in the DM1 group than in a sample of healthy controls. Neuropathy may be one of the explanations for some of the pain reported in adult patients with DM1.

5. Discussion

5.1 Main Findings
In this study, we have documented trunk muscle impairment in adult DM1 patients. The impairment was related to CTG size and disease duration. In addition, it was related to walking capacity measured by 6MWT, general mobility measured by RMI and balance measured by TUG. We also documented possible mechanisms behind the trunk muscle impairment by MRI. Muscle fat infiltration and atrophy were significantly more prevalent in the DM1 group compared to the healthy age and gender-matched control group. The myopathic changes in the DM1 group were related to MMT, RMI, TUG and respiration measured by FVC. Furthermore, we documented a high frequency of chronic pain (84%). The pain was widespread and symmetrically distributed, with low back pain being the most frequent location (40%). Pain intensity was related to respiration, quality of life (WHO QOLBREF), fatigue, measured by the FSS, disease duration, measured by the number of years diseased, and the CTG size. Important gender differences regarding frequency and intensity of pain, as well as how pain was related to function, was documented. Women had the highest pain intensity and more pain locations. Furthermore, more women had low back pain. In women, pain intensity was related to activity, respiratory function and BMI, while in men, the number of pain locations were related to WHO QOLBREF and psychological functioning. Neuropathy and symptoms of neuropathic pain was seen in a few patients, and may be a part of the pain experienced in DM1.

5.2 Trunk muscle impairment-frequency and severity
In our first study, we document relatively early, trunk muscle impairment in DM1 adult patients. Both back and abdominal muscle strength were below normal (MRC 0-3, < grade 3) in 75% and 95% of the participants, respectively. More than 50% of the patients had severely
impaired strength (MRC 0-3, <grade 2) for trunk flexion, while 5% had severely impaired trunk extension. Using new analysis of muscle strength measures, these findings were confirmed in the total sample of patients (n=50), except from the back-extension impairments of severe degree. This increased from 5% to 12% (see Figure 3), while back and abdominal muscle strength below normal were 78% and 94%, respectively. We also noted that the results of the mean muscle strength from the first paper remained consistent throughout the whole patient group, see figure 6. This demonstrates that the muscles are equally impaired compared with the pattern of involvement shown in the first paper.

**Figure 6. Muscle strength below 2 in %, and mean muscle strength (MRC 0-3) in the N50 group of patients**

Figure 6. New results from analysis in the total number of included patients (N50). Mean muscle strength is presented for all functions tested (blue bars), and severe muscle weakness (MRC<2) in % for the most impaired functions (red bars).

Paresis and myopathy in adult DM1 are expected to start distally in the extremities [3], as reflected in the DM1 disease specific muscular impairment rating scale (MIRS). MIRS is one widely used assessment tool for progression of motor involvement in DM1, but it does not include monitoring or scoring of the abdominal and back muscles [41]. In fact, due to the presumed absence of proximal muscle involvement, DM1 has been categorized as a distal myopathy, as opposed to myotonic dystrophy type 2, which is categorized as a proximal myopathy, [2]. To our knowledge, our study is the first to explicitly focus on trunk muscle function clinically in DM1. A few recently published MRI studies have documented fat infiltration in abdominal and back muscles [38, 49, 50]. In addition, in a recently published paper by Witting et al., axial myopathy is considered to be an overlooked clinical feature of hereditary muscle diseases [119].
5.2.1 Relation to walking, mobility and balance.
We further showed that trunk muscle strength was strongly related to walking capacity, mobility and dynamic balance, measured by 6MWT, RMI and TUG respectively. Since our study is the first clinical investigation of trunk muscle strength in adult DM1 patients, we cannot compare our results with other DM1 studies. However, from studies on the general population, trunk muscles have been proven to be especially important in postural stability [25]. And even though some argue that muscle strength is less relevant for stability than timing and co-contractions, a certain amount of muscle strength is needed [46]. In an MRI study of facioscapulohumeral muscular dystrophy (FSHD), which is a muscular dystrophy that impairs both extremity and trunk muscles, postural stability was more related to trunk muscles than muscles of the extremities [120]. In our study (paper I), muscle strength in the trunk was slightly stronger related to both walking and balance, compared to strength in the lower extremities. That muscle strength in the extremities is related to motor function has been discussed in previous studies on DM1 [68, 84]. Hammaren et al. showed that TUG was related to muscle strength in the lower extremities, but this study did not include trunk muscles [68].

An increased risk of falls is seen in DM1, and more knowledge on the reasons for falls in DM1 patients is needed [71]. Our clinical experience of falls and its consequences, such as fractures and incomplete recovery, strongly support the need for such research. The results from our study on how weakened back and abdominal muscles are associated with reduced balance and mobility, may be relevant for understanding the risk of falls in DM1 patients.

5.3 Myopathy in Trunk muscles
To investigate which mechanisms were behind the impaired muscle strength seen in study I, we pursued our findings with an MRI study. We investigated muscle fat infiltration and atrophy in abdominal and back muscles, and in the psoas and gluteal maximus muscle. The two latter muscles are important stabilizers in trunk flexion (the curl up), and trunk extension, which were the strength functions measured [27]. We also investigated whether MRI findings were related to motor function, CTG size and disease duration. Which muscles were involved and the degree of myopathy was described. Since muscles work in synergy, impaired muscles may be compensated for, and therefore the degree of myopathy can be camouflaged, resulting
in normal muscle strength when measured by the MMT. The MMT has broad categories and is less sensitive to small changes of strength [80]. Muscle MRIs have shown that the soleus and the medial head of gastrocnemius muscles are the muscles with the highest degree of fat infiltration in DM1 patients' lower extremities [44]. On the other hand, the dorsal flexion of the ankle has been shown to be the most impaired function in DM1 patients [79]. This may be an example of how synergy, in this case, the rest of the strong triceps muscles in the leg, may compensate for myopathic muscles, and provide good strength. Bassem et al. [121] have shown that there is a relationship between DM1 myopathy in the tibialis anterior muscle and dorsal flexion strength of the ankle.

5.3.1 Muscle MRI: Fat infiltration and atrophy

The MRI results documented significant, large, case-control differences in muscle fat infiltration and atrophy, indicating myopathy caused by DM1 [122]. DM1 mainly affects muscle fiber type I [29]. As trunk muscles have more type I muscle fibers than type II [28, 123], trunk muscles may be more vulnerable to DM1 pathology.

The studied trunk muscles were differently affected. Some were severely fat infiltrated, while some were moderately or mildly infiltrated. Interestingly, the psoas muscle had no fat infiltration. The psoas muscle is a stabilizer of the back, but it is also a powerful mobilizer of the hip. One study documents a predominance of type II fibers in this muscle. However, this depends on which level of the muscle is investigated [124]. But this could be an explanation for a relative sparing in DM1. We investigated the psoas muscle at the L4/L5 level, where the function is more related to the hip and the hip’s mobility than the more proximal part of the psoas [27]. In a longitudinal study on the progression of muscle strength in adult DM1, hip flexion remained stable [125].

The findings of severe muscle fat infiltration in trunk muscles were in line with a few other MRI studies on DM1 patients, which included some of the trunk muscles we investigated [39, 50, 126]. However, some of these studies did not limit inclusion to the adult DM1 forms, and congenital and childhood forms may have been included [39, 126]. Generalized hypotonia is a symptom in the congenital form, which may indicate more general muscle involvement [3]. Compared to these previous studies, we investigated different muscle levels in the lumbar erector spinae and the abdominal rectus, and included the oblique and transvers abdominals. Furthermore, muscle size in trunk muscles was, to the best of our knowledge, measured for
the first-time in DM1. Another novel contribution was the case-control design, with age and gender-matched controls. A case-control design is suited for rare diseases and small populations, and allow for conclusion on differences between healthy persons and persons with DM1. However, level of exercise is not controlled for in the two groups. Exercise influences muscle size and function, but it does not influence levels of muscle fat infiltration in healthy muscle tissue [33].

5.3.2 MRI results: relation to mobility, balance and FVC

The MRI results in the abdominal and back muscles showed different associations with function. The abdominals were significantly related to motor function (abdominal strength, RMI, TUG and FVC), while the back muscles showed tendencies towards an association with RMI, though this did not reach significance. The back muscles were only investigated at the lumbar level, which may have influenced the lack of association with motor function. RMI and TUG are assessments which demand trunk muscle function working against gravity, including higher levels of the back extensors. Another MRI study on DM1 patients found that back extensor muscles at the thoracic levels were highly infiltrated by fat [50]. The 6MWT was not related to MRI findings in either abdominals or lumbar back muscles. The proximal muscles of the lower extremities in DM1 patients are the strongest [9], and may thus carry most of the workload in walking. Another MRI study on DM1 patients investigated muscle fat infiltration in the back extensors at the thoracic, as well as lumbar levels of the vertebral column. In that study, the results from a sum score of all the back extensors were related to the 6MWT, while a sum score of the extensor group, as well as the flexor group, were significantly correlated with cobb’s angle, which is a sign of scoliosis when >10 degrees [50].

Muscle fat infiltration in the abdominals was related to activity in our subjects, which demands more general mobility (RMI) and balance (TUG). On the other hand, the muscle size of the abdominals was the measurement most related to muscle strength. This was demonstrated by the association between muscle size in the rectus abdominus and trunk flexion measured by the curl up as well as respiration measured by FVC. In these two functions, the rectus abdominis muscles have a primary mover function [27]. Especially important was the correlation between muscle size in the abdominal rectus muscle and respiration in our study (paper II). A lack of association between respiration and motor performance in DM1 has previously been emphasized in the DM1 literature [42, 47]. That muscle strength and respiratory values have shown no association may have been influenced
by DM1 being categorized as a distal myopathy [2]. Another reason may be the lack of evaluation of trunk muscles in DM1 studies using MIRS to evaluate muscle strength [41]. Indeed, Kierkegaard et al. highlight that there is no relationship between respiration and the severity of muscle impairment, based on the DM1-specific muscular impairment rating scale, MIRS [42]. However, in a study on respiration in DM1 patients, where the rectus abdominus muscle was included, myotonia and strength impairment in respiratory muscles were demonstrated by EMG, as was restrictive respiratory deficits [48]. While the diaphragm is the main inspiratory muscle, the rectus abdominus is the primary mover in forced expiration [27, 127]. Trunk muscle impairment may also lead to a stiffened trunk, kyphosis, and scoliosis. Such impaired mobility may reduce both inspiratory and expiratory values [128, 129].

Impaired respiration is one of the main causes of death in DM1 patients [130, 131]. Consequently, knowledge on the muscles involved in DM1 that may influence respiration is important.

5.3.3 Relation between trunk muscle impairments, MRI measures and CTG size
The trunk muscle impairment documented in this study was significantly correlated with the number of CTG repeats. This indicates that this finding may be caused by DM1. Previous literature reports a variable genotype-phenotype relationship between CTG size and muscle strength in adult DM1 [9, 10]. Therefore, caution must be taken in predicting clinical severity based on CTG repeats [11]. In our sample, the relationship between trunk muscle involvement and CTG size is high (r= -0.64, p<0.001). One possible reason may be that CTG size was reassessed at the same time as the strength measurements were performed. On the other hand, the MRI measurements of fat infiltration and muscle size were not significantly related to CTG size. This may be caused by the mosaic expressions of CTG size in different tissues. We investigated CTG size in blood cells and the number of repeats are higher in muscle tissue than in blood cells [16].

5.4 Pain
In study III, we found that as many as 84% of the patients experience chronic pain, which is substantially higher than in studies on the general population [132, 133]. This finding has also been reported in other studies on pain in neuromuscular disorders, which included DM1 patients [62, 64, 66]. However, in a review comparing myotonic dystrophy type 2 and DM1,
DM1 is described as painless [2]. We found that the number of pain locations were 3.2, symmetrical and widespread in the body. The most frequent sites were the lower back, neck and hands. This finding has also been reported by others [65]. Thus, for frequency and locations, our results confirm previous findings [62, 65, 66]. Previously published studies on pain in DM1 are mainly surveys, sent by post to mixed groups of patients, and not primarily to people with a genetically verified diagnosis [62, 64, 65]. Our paper, confirming these findings, is of importance given our observational study design, the well-defined DM1 group and the fact that we reassessed the CTG size. We also combined pain assessments with a clinical examination of function. In addition to confirming previous findings, we document additional new information regarding how pain was related to gender and to other symptoms in DM1 patients.

Interestingly, pain intensity in the whole patient group was significantly correlated with the CTG size, which may indicate that pain is a consequence of DM1. This has, to our knowledge, not been documented by others investigating pain in DM1 [62-66]. Our results are also strengthened by the fact that pain assessment and genetic testing was done simultaneously [6]. We documented a significant association between disease duration and pain. Pain seems to slowly increase according to disease duration, which has been described before [64].

The most frequent pain location was the lower back, also previously reported by others [62, 65]. Although, we did not find a relationship between muscle strength and pain, it is plausible that the myopathic process in the trunk muscles may lead to pain. In our study, we documented edema in several trunk muscles, and almost complete fat infiltration in the lower erector spina and the cranial rectus muscles of some patients. Our MRI results also showed that edema was more frequently present in DM1 patients (45%) compared to the control group (5%). Edema, as well as high levels of muscle fat infiltration, may be a symptom of ongoing muscle damage [101]. Tissue damage, in this case, trunk muscle damage, could cause nociceptive pain [59]. Furthermore, in sarcopenia, in which muscle wasting resembles DM1, atrophy may lead to pain [134, 135]. Loss of muscle strength and atrophy in trunk muscles may lead to impaired postural stability, and thus to injuries and musculoskeletal pain [46]. Muscle biopsies in DM1 patients show centrally located nucleus in the muscle fibers, a sign of constant regeneration [20, 37]. In addition, adipose tissue itself may be part of an inflammatory pathway of nociceptive pain [134].
5.4.1 Pain and gender

A novel contribution in our study is the gender difference. DM1 women report significantly higher pain intensity and number of pain locations compared to DM1 men. Another important finding was the different relationships between pain and function in the two genders. Women’s pain was related to motor function, respiration and BMI, while men’s pain was related to the autism quotient and quality of life. The reason for this is unclear. It might be that DM1 affects the genders differently. One previous study documented different symptoms in female and male patients. Men more often have CNS affection, myotonia and live isolated lives. Women, on the other hand, have more frequent bowl problems, obesity, and cataracts [136]. Another explanation may be sex differences regarding muscle tissue. DM1 women are more weakened by the disease with time than DM1 men [125]. In general, muscle size in men is larger, and muscle fiber type I occupies a larger part of women’s back muscles compared to men’s [31]. Given these sex differences, one might speculate that back muscles in women are more vulnerable to DM1 pathology, especially in the light of fiber type distribution [29]. It may also be that the women in our study were more affected because of higher levels of CTG repeats. However, when controlled for by a regression analysis, where pain was the dependent variable and CTG size and gender were independent variables, only gender contributed significantly to pain (β:0.39, p=0.008) On the other hand, both Katz ADL and FVC were strongly related to CTG size. CTG may therefore be a confounder to the relationship between pain; and activity and respiration in women.

The observed gender differences may have implications for interventions. Both motor and psychological functioning may be important aspects of pain management in DM1. A combination of such strategies has been successful in DM1 patients with fatigue [137]. Fatigue is related to, and predicted by, pain in DM1 patients [64]. Furthermore, these gender differences should be accounted for in future studies on pain in DM1.

5.4.2 Neuropathic pain?

In our last study, we investigated neuropathy and the possible presence of neuropathic pain. The pain intensity and the distribution of pain in the hands and feet could indicate that this is a phenomenon in DM1 patients. Neuropathy has previously been demonstrated in DM1.
However, small-fiber neuropathy as shown by skin biopsies and IENFD, has to the best of our knowledge, not previously been documented in DM1 [138].

By using three different methods to investigate peripheral neuropathy (Quantitative sensory testing, skin biopsies measuring IENFD, and neurography), we identified neuropathy in 50% of the patients. Description of pain sensations, like burning or lancinating pain in hands and feet, was present in 30% of the patients. An overlap between these descriptions of pain experience, sensory deficits and objective and semi objective findings of neuropathy was present in 15% of the patients. This is higher than documented in the general population [139]. We did show significant different IENFD in patients compared to healthy controls, indicating subclinical small fiber neuropathy in the patient group. This may explain that only half of the patients reporting neuropathic pain presented with findings on neurography or quantitative sensory test.

There is a possibility that the DM1 patients who were most bothered by pain were more motivated to accept the invitation to participate in this part of our study. However, the frequency of pain reported in this patient group was 90%. Other studies on pain in DM1 patients report pain frequencies between 60-88% [62, 63, 65, 66]. In our third study, which included 50 persons, we found that 84% reported chronic pain. Another possible cause of neuropathy is diabetes or hormonal changes. However, none of the participating patients had a diagnosis of diabetes or hypothyroidism.

5.4.3 Pain and fatigue and quality of life

Pain is a subjective experience, and an association with emotions, like anxiety and depression, is well-known, also in DM1 patients [63, 140]. Therefore, we included measurements of anxiety and depression. However, these were not related to any of the pain measurements. This may be caused by the fact that the measures BDI and BAI exhibited a floor effect, and showed little variation. We documented significant association between pain and both QOL and fatigue. The association with QOL indicates that pain may be one of the causes of lower QOL in adults with DM1. The most bothersome symptoms reported by DM1 patients are fatigue and pain, and pain is found predictive of fatigue [64]. Winblad et al. document that muscle impairment and depression are correlated to fatigue in DM1 [109]. In study IV we show that fatigue was significantly associated to neuropathic pain, neuropathy may thus play a role in fatigue in DM1 as well.
Awareness of the fact that pain in DM1 patients may be caused by different mechanisms is important in clinical follow-up, and in future studies on intervention.

5.5 Methodological considerations

5.5.1 Study design

The cross-sectional design used in study I, III and IV enabled us to collect data at one point in time, and is therefore relatively fast and cheap. It is also well suited for our study questions as we wanted to investigate the presence of trunk muscle impairment, the presence of pain, gender differences in pain and neuropathic pain. That being said, the cross-sectional study design also has limitations. It is not well suited for clarifying which direction associations go, or the degree of progression, since it only involves one measurement point in time. However, we also wanted to know if disease duration was related to our main findings. Disease duration was therefore calculated based on the patients’ own reporting of their first symptom. This is dependent on memory, and might be subject to recall bias.

In study II, we used a case-control design which enabled comparison between patients and healthy age and gender-matched controls. This strengthens our conclusions about the mechanisms responsible for the documented clinical weakness. Both age and gender may influence the outcome variables in this study. Therefore, age and gender matched groups were important to counteract confounding. However, since the design is at one time point it is not suitable for studying disease progression.

5.5.2 Statistical considerations

**Type I and type II error**

Type I error is when null hypothesis is rejected wrongfully. The p level is a number reflecting the probability of such an error. In this study, our p level was set at 0.05, and was Bonferroni corrected according to numbers of comparisons in our hypothesis testing. When we conducted explorative analyses, correction was not done, thus caution must be taken when these results are interpreted. Type II error is when null hypothesis is kept based on wrong findings (false negative). The power of the study indicates the probability of such an error. Power is strengthened by the number of patients included and by the sensitivity of the measures. In this study, power was set between 80-90% for hypothesis in the pain study and 95% in the MRI
study, which is acceptable. DM1 is a rare disease, and high numbers of included patients is difficult in a short period of time in a country like Norway, where a small population live geographically spread. Thus, small associations were not detected as significant findings. Consequently, we calculated Cohen’s d, when possible, to assess the magnitude of the effect and we may speculate whether the findings would have been significant in a larger sample. And, for some of our findings this was the case (e.g. paper II: Cohens d >0.5 for muscle size in back extensor muscles level L1/L2 and L3/L4).

We used both parametric and nonparametric statistics dependent on the type of data and the distribution. In paper I only parametric analysis were performed, however, all analyses in this paper were also controlled with non-parametric analysis, which did not change the results or conclusions.

Most measures used were previously used in DM1 studies (AQ and IENDF has, to our knowledge, not been used previously). However, not all were validated, and reliability-tested in DM1 patients. Some measures of pathology showed low variation and sealing or floor effect. This was especially the case for KATZ ADL, the BAI and the BDI. For these measures, we used nonparametric analyses. These measures may camouflage findings, and cause a type II error. The MMT MRC 0-3 has broad categories to ensure stability (intra and inter-rater reliability). However, this leads to less sensitivity. The MMT measure is not recommended for use in evaluating small effects, but for our goal, which was to detect pathological levels of strength, it is considered reliable and valid [78, 80].

5.5.3 External validity

External validity is about the generalizability of study results to a larger population, which the study population is intended to mirror. It is influenced by the representability of the study sample, and by internal validity. Study samples may be different from the larger population due to selection bias, which in turn is influenced by how the patients were included, and where. However, in this study, we tried to include a random group of adult DM1 patients within the inclusion and exclusion criteria, which to some degree were different in the four studies. We sought to counteract inclusion bias through a variety of invitation channels. We promoted the study in three different ways: through specialist hospitals working with the group, through the patient organization’s own journal, “Muskelynntt”, and through the national register on inherited neuromuscular disorders. If we had only included patients who were
already being followed at a hospital, we may have ended up with a patient selection biased towards more severely affected patients. However, since information also reached persons who were not necessarily being followed at specialist hospitals, we believe less affected persons with DM1, as well as some with hardly any symptoms, were recruited. Our inclusion strategy was consecutively inclusion until we had added the number of patients necessary. Five of 55 patients declined the invitation to participate. Fatigue, avoidant personality and different levels of disability may be symptoms of DM1 [42, 64]. We tried to counteract this by calling and reminding the patients of the invitation sent by regular mail. We were also available to answer questions and ensure that the participants knew they could park the car close to the hospital, that they would be able to rest during the experiments, and that they would be served food and beverages during the day. This may have contributed to the high response rate at >90%.

Since 27 of the 50 patients included came from Buskerud county, we compared measures of disease duration, CTG size, gender, age and mean muscle strength in this patient group to the other population (n=23). These were patients included from several other counties in Norway (south-east and northern Norway), and we did not find any significant differences between the patient group from Buskerud and the other counties.

The samples in the different studies were compared to the rest of the main N50 group. When comparing the MRI sample with the main sample, disease duration was different (p=0.022, mean difference -5.9, t=-2.4 (CI=-10.9- -0.8)). The patients in the MRI study had shorter disease duration, which may indicate that this sample has less severe disease. The specific exclusion criteria in the MRI study may have influenced this. Study III was a pain study, but many patients who participated were also participating in study I and II. This may have prevented only patients interested in pain from participating. However, study IV mainly focused on pain and neuropathy. This may have been a bias in that interested patients suffering from such symptoms may have wanted to participate. These findings should therefore be interpreted with some degree of caution. However, the population in study IV did not differ significantly to the rest of the subjects in the N50 group with regards to CTG, age, and disease duration. Furthermore, the group included in study IV differed little regarding pain frequency compared to the main N50 sample (90% versus 88% respectively).
We think the whole sample is representative for the adult forms of DM1, though caution must be exercised as a certain degree of effort is needed to respond to invitations for studies. This may bias the sample to a less affected patient group. On the other hand, some of the patients were introduced to the study through their physicians or other members of their family, and thus patients with more severe symptoms also managed to respond. Caution must also be taken in generalizing to an asymptomatic DM1 population, since almost all included patients presented some clinical symptoms. We found that the female patients in our study had higher levels of CTG repeats and longer disease duration than male patients. It is possible that the more severely affected men are more isolated or die earlier compared to female patients, as described in the literature [136]. On the other hand, less affected women may be less motivated to participate in such studies.

5.5.4 Assessment, reliability and Internal validity

The reliability is about the repeatability of the study, and dependent upon the internal validity of the study. Internal validity is how well the results actually represents the included and studied patients [141]. Internal validity is influenced by the study design, the measures and information bias.

*Information bias:* One possible biased information was the reports on time of first symptom, which is dependent on memory. Several other measures were based on interviews and subjective reports, which may also be biased. However, an exclusion criterion in our study was mental retardation. An IQ within normal variation ensured better memory and ability to report.

One strength of our study is that we combined subjective reports from the patients with measures from clinical assessments performed by different clinicians with relevant specialties within the neuromuscular field. The study protocol was extensive and could cause exhaustion in this patient group. We tried to counteract this by offering the participants to rest between the different measures if they felt they needed this. The order of measures within the different procedures was equal for all participants, however whether they started with the psychological or neurological or motor examinations varied. For some measures (neurological, neurophysiological and psychological) more than one person performed the examinations, this can have influenced the results. On the other hand, all professions who examining the patients were experts and experienced in their field. For the motor function
measures one person (the PhD candidate) examined all the patients. Interrater reliability analysis was conducted for MRI analysis and MMT and found excellent.

Another strength was the new calculations of CTG repeats at the time of inclusion. This is important, since CTG repeats may change during the patients’ lifetime. Also, since CTG repeats may differ in different tissues due to its mosaic expression, we have discussed this phenomenon when there is a lack of significant association between CTG repeats and other measures.

*Measures:* Most chosen measures are standardized and previously used in studies on DM1 patients. Not all of the measures were evaluated in DM1 populations, however some main measures were: TUG, 6MWT, MMT:

**MMT:**
A recent review documented good validity and reliability for MMT in DM1 patients. However, it commented on some known limitations regarding discrimination between grades, the width between the grades, and the dependence of the skills and strength of the person who examines the patient [80]. In our study, we recoded the MRC scorings 0-5 to MRC 0-3 scorings according to Vanhoutte et al., see table 3 [81]. This was done to counteract the addressed limitations of the MMT in discriminating between the scores, and to be able to use the scale as an interval scale [81, 142]. The measures were performed by an experienced physiotherapist in this field (the PhD candidate). Furthermore (13 %) five of the 38 patients in paper I were doubly scored by another experienced testers, and full agreement was achieved. When trunk flexion strength was tested, we adjusted the procedures for some. For patients with neck flexion strength below the ability to move against gravity, grade 2 (MRC 0-3), their head and neck were supported and stabilized, to enable the test and prevent injuries. This may have led to higher scores for these patients. Adjusting stabilization in accordance to individual needs in muscle strength testing is a common and recommended procedure. For example, when back muscle strength is tested, stabilization is moved from the proximal part of the lower extremities to the pelvis if the patient has weakened hip extensors [27, 119]. Pain may limit muscle strength, though none of the patients reported pain as a limiting factor when trunk muscles were tested. Another limiting factor to muscle strength may be joint contractures [27]. None of the patients had a diagnosis of scoliosis, and none had contractures in the joints of the extremities. There were a few who had tendencies towards increased
thoracic kyphosis. However, these were not passive mobility limitations, except for one person who had experienced vertebral fractures after a previous fall.

TUG:
An important difference between our TUG results compared to others, [42, 68, 86] is that mean TUG time was lower (patients walked faster) in our study. This may be caused by our instruction of “perform as fast as possible, but safely”, instead of just “safely”. The reason for this instruction was to be certain of equal understandings of the test, while also increasing motivation. Speed might also improve performance in a group of patients where type I muscle fibers are primarily affected [2]. The psychometric properties of TUG were investigated in a small group of DM1 patients, and TUG was a recommended test of balance performance in DM1 patients. Static tests of balance, like tandem stands, showed low test-retest stability [71, 80, 86].

MRI:
In the MRI study (paper II), we used two independent, experienced radiologists to control for the reliability of the scorings, which were done manually, for muscle fat infiltration and muscle size. The inter-rater reliability was found to be excellent between the two.

5.5.5 Confounders
Confounders are phenomena biasing the conclusions by acting upon both exposure and outcome measures. We discussed different possible confounders and controlled for them by stratification or by using regression models in our analysis. We used regression models in paper II and III. One important possible confounder regarding gender differences was the CTG size, since it was different in men and women. We therefore controlled for this by regression models, and showed an association for some of the motor function measures (FVC, KATZ) related to pain in women. We further discuss the possibility of unknown confounders regarding the relationship between AQ and pain in men. There may be a common cause, such as CNS affection or reporting style. One other concern is that we did not have information on how physically active the individual participants were. This would have been an interesting measure with regards to impairment of trunk muscles, fat infiltration and atrophy. In spite of this, we do think the degree of fat infiltration compared to the control group, and the association between trunk impairment and CTG repeats, support the conclusions that myopathy and trunk muscle impairment may be caused by DM1.
5.5.6 Ethical considerations

All the participants gave their written consent to participate in each study. The study was submitted and approved by the Regional Ethics Committee for health research region South East (REK# 2011/2186). Additional approval for carrying out the study on pain in DM1 (#2015/2364) and muscle MRI (#2015/2354) was obtained. Genetic testing was only done on patients with a previously confirmed diagnosis. Only the DM1 relevant region of chromosome 19q was analyzed, ensuring no unintentional genetic findings would be made. Clinical findings in each patient were followed up with the necessary treatment and intervention in the ongoing rehabilitation program. Participation did not affect the normal follow-up. Coincidental MRI findings in the participating controls were handled by a physician. All information collected was stored in the patients’ own hospital files. Information in the SPSS file was anonymized by ID number. A list linking ID numbers and names was securely locked in the hospital archive accessible only to accredited members of the research group.

6. Conclusion

6.1 Summarized

Trunk muscle impairment and myopathy, related to important motor function was prevalent in DM1. Furthermore, pain was frequent, and different in men and women, and may be related to different associated DM1 symptoms. Neuropathy might be a part of pain in DM1. The number of CTG repeats and disease duration was associated with pain and trunk muscle affection, which supports the conclusion that these findings may be caused by DM1. It is important to include trunk muscles and pain in follow-up programs of DM1. Gender must be accounted for in future studies on pain. Trunk muscles should be further investigated, given their role in respiration, mobility, balance and possible pain.

- Trunk muscle impairment was documented by the MMT and it may be both severe and present relatively early.
• Trunk muscle strength in DM1 was related to walking, as measured by the 6MWT, general mobility assessed using RMI and balance, as measured by TUG.

• MRI findings, showing large, case-control differences in fat infiltration and atrophy, strengthen the likelihood of myopathy in these muscles being driven by DM1 pathology.

• Different aspects of myopathy including fat infiltration, atrophy and edema, are to the best of our knowledge, for the first time, documented using MRI in DM1 trunk muscles. Fat infiltration and atrophy was related to different motor function.

• CTG size was strongly correlated to trunk muscle impairment.

• Pain in DM1 is observed in 84% of patients. Pain was related to the CTG size, disease duration, fatigue, quality of life and respiration. It was widespread and symmetrical throughout the body. The most frequent locations were the lower back, neck, hands and feet.

• Gender differences in pain are likely described for the first time in this study. DM1 women had a higher intensity and more pain locations than DM1 men. In addition, pain in women was associated to BMI and motor function, while pain in men was related to psychological function.

• The motor function related to pain in DM1 was functions involving trunk muscles activity, and respiratory function, which involves the m. rectus abdominus, in particular. The psychological measure associated to pain in men was the autism quotient.

• Neuropathic pain was reported by 30% of the patients. Neuropathy was present in 10 of 20 patients. 15 percent report neuropathic pain in addition to clinical sensory findings and objective and semi objective findings indicating small or large fiber neuropathy. Neuropathy in DM1 patients has been described by others. However, we are to the best of our knowledge, the first to compare findings of neuropathy to the
patients’ own reports of neuropathic pain and to study small fiber neuropathy assessed by skin biopsy in patients with DM1.

6.2 Clinical perspectives

Based on the findings from this study we suggest adjustments to the follow up programs of DM1 patients: Assessments of abdominal and back muscle strength should be done by routine. Associated findings with trunk muscle impairments: respiratory deficits, impaired balance and mobility should be attended. Investigation of the presence, intensity, quality and location of pain should be included.

6.2 Future studies

We suggest future studies to address the following issues:

- Progression of trunk muscles impairments and myopathy by longitudinal studies.

- Effect studies on trunk muscle intervention using respiratory values, mobility and balance and pain as outcome measures.

- Longitudinal studies of pain accounting for gender differences are needed.

7. References


the 3’ end of a transcript encoding a protein kinase family member. Cell. 1992;68:4799-808.


based study with implications for disease classification. Rev Neurol (Paris). 2016;172
10:572-80; doi: 10.1016/j.neurol.2016.08.003.
58. Kalkman JS, Zwarts MJ, Schillings ML, van Engelen BG, Bleijenberg G. Different types of fatigue in patients with facioscapulohumeral dystrophy, myotonic dystrophy


Major involvement of trunk muscles in myotonic dystrophy type 1


Objectives – The motor impairments in Myotonic Dystrophy 1 (DM1) are assumed to progress from distal toward proximal parts of the extremities in the Juvenile and Adult forms of DM1. On occasion and late in progress spine deformity is observed. In this study we have examined whether and to what extent trunk muscles are impaired in DM1, and if this impairment is correlated with the duration of the disorder, walking capacity, mobility, balance, and CTG-repeats.

Materials & methods – Manual muscle testing (MMT) of skeletal muscle strength in trunk and extremities, reassessment of the mutation size, time since first symptom, the 6 min walk test (6MWT), Rivermead mobility index (RIM) and Timed up & go (TUG) were sampled in 38 adult DM1 outpatients.

Results – We found significant impairment in trunk muscles. Trunk muscle strength decreased significantly with increasing mutation size (r = −0.64, P < 0.001). Reduced walking capacity, mobility and balance were significantly related to decreased trunk muscle strength. Conclusion – DM1 affects trunk muscle groups. The trunk impairments seem to occur relatively early in disease progression. Awareness of trunk impairments may be of importance for everyday functioning and for understanding the risk of injuries due to falls reported among DM1 patients. It may also help in identification of DM1 patients and considered outcome measure in future clinical trials.

Introduction

Myotonic Dystrophy 1 (DM1) is a progressive autosomal dominantly inherited multisystem disorder caused by a CTG nucleotide repeat expansion in the Myotonic dystrophy protein kinase (DMPK) gene in chromosome 19 (1–3). It is one of the most prevalent neuromuscular disorders affecting about 1 in 8000 (2). The motor impairment in DM1 is documented to progress from the distal to the proximal part of the extremities. Early involvement of the face and anterior neck muscles are also common (2, 4–7).

Spine deformity and general weakness in Juvenile and Adult forms of DM1 are anecdotally reported to occur late in DM1 progression (4), but no systematic investigation of strength in trunk muscles are documented. The disease specific motor impairment scale (MIRS) (5) which is recommended in the Scandinavian reference program for DM1 does not include assessment of trunk muscles (8). The research team has observed that DM1 patients frequently display abnormal alignments and decreased movements in the trunk during walking, indicating muscular impairment in this part of the body. These clinical findings led us to systematically assess strength in trunk flexor muscles and back extensors. The need for systematic evaluation of trunk muscle strength is underscored by pathological (replacement of muscle by connective tissue and fat) MRI findings in m. Rectus abdominis and m. Erector spinae muscles in a small DM1 sample (9). Strength in trunk muscles is of importance for everyday life through its stabilizing role in mobility and balance (10). A Swedish study of balance and falls leading to injury in DM1 patients highlights the importance of several tests for information about different aspects of postural control in DM1 (11).
The aim of this study was to detect whether and to what extent trunk muscle groups are impaired in DM1 patients and to investigate the progression of muscular impairment in these patients by relating muscle strength to disease duration. Furthermore, we wanted to examine whether strength in the various muscle groups is correlated with the number of CTG repeats and walking capacity, mobility and balance measured by the 6MWT, Rivermead mobility index (RMI) and Timed up and go (TUG).

Material and methods

Standard protocol approvals, registrations, and patient consent
All included patients gave their written informed consent to participate and the study was approved by the Ethic committee of Norwegian Health authorities, region South East.

Participants
All patients above the age of 15 with a genetically confirmed diagnosis of DM1 and referred to the Department of Habilitation at Drammen hospital between 2012 and 2014 were asked to participate in the study. Among these, 23 of the patients were referred from local neurologists for regular follow-ups, seven patients were recruited for this study through Oslo University Hospital and eight through the patient organization. The congenital form of DM1 was excluded because of the different clinical characteristics compared to the other (4). Two patients declined to participate, 38 patients were thus included.

Study design
The present study has a clinical observational design combining data from interdisciplinary clinical examinations, standardized assessment tools and new measures of the CTG expansion. Information about time of first DM1 symptom is based on retrospection. Evaluation of progression of disease is done by cross-sectional analysis.

Procedure
An experienced neurologist performed the examinations according to a standardized clinical protocol, allowing collection of neurological history and neurological examination and information about current medication. The measures of strength and function were performed by an experienced physical therapist with 13% (all muscle groups in 5 of 38 participants) scored independently by another experienced tester and full inter-rater agreement was achieved.

Measures

Age at onset – Determined by questioning the patients about age at onset of at least one of the following well-known DM1 symptoms and signs: difficulty in walking or running, fine motor problems, difficulties loosing grip, swallowing difficulties, decreased strength, stiffness, cataract, arrhythmia or episodes of apnea (12).

DM1 subgroup – DM1 subgroup was determined by age at onset; Childhood form: onset between 1 and 10 years, Juvenile form 11 to 18 years, Classic adult form: 19 to 39 years and Mild adult form: first symptoms after the age of 40.

Disease duration – Defined by difference between age at onset and age at the time of examination. Four disease duration groups were defined based on the distribution of disease duration in our sample with the principal aim of as equal group sizes as possible: Group 1: <11 years \( (n = 10) \), group 2: 11–17 \( (n = 10) \), group 3: 18–27 \( (n = 10) \) years and group 4: more than 27 years \( (n = 8) \).

CTG expansion – All participants were previously genetically confirmed DM1 patients. Expansion size reassessment was done using Southern Blot analysis of lymphocytes in order to have information about mutation size at the time of clinical examination.

Skeletal muscle strength – Muscle strength was assessed with the standardized MRC 0–5 scale for MMT (13). This procedure has been used in previous studies of muscle strength in trunk muscles groups in neuromuscular diseases (14). MMT is chosen over Quantitative Muscle Test (QMT) in this study since the MMT is an easy and inexpensive way of measuring trunk-muscle strength in the clinic. MMT is an accepted method and has been found reliable for evaluating muscle strength (13, 15, 16). It has been criticized for its unequal width of its response options, providing only ordinal data, and for physicians inability to discriminate between the categories, especially grade 4 and 2 (17–19). To counteract these limitations, the MRC 0–5 scale was rescored to a modified 0–3 scale according to Vanhoutte et al. (19). By Rasch modeling of strength measure data from 1065 patients with different neuromuscular disorders (including DM1), Vanhoutte et al. (19)
documented reliability, and restored thresholds enabling the modified 0–3 scale to be analysed as an interval scale. All muscle groups tested in our study, including the trunk flexors and the back extensors, were included in the Vanhoutte study (Table 1).

Test positions were used according to standard MMT (20). Joint mobility, muscle length, and pain that could influence strength assessment were controlled for. Strength was measured twice with a 3 min interval, reporting the mean of the two. The 11 muscle groups in the DM1-specific MIRS were tested, except for the plantar flexion of the ankle and finger flexors (5). The plantar flexion of the ankle is known to be less affected than the dorsal flexion, therefore this test was excluded due to risk of exhaustion (6). Grip strength is not suitable to measure with MMT (20). Our dynamometer-data on grip strength is thus not included in this report for simplicity purposes. The following muscles were measured: In the upper limb, three proximal muscle groups (shoulder abductors, elbow flexors, elbow extensors) and one distal group (wrist extensors). In the lower limb, three proximal groups (hip flexors, knee flexors, knee extensors) and one distal group (foot dorsal flexors) were tested. Due to reported symmetry in DM1 (6) and to prevent exhaustion, only the dominant side was tested. In addition, the anterior trunk flexors and the back extensors were tested. For grading of muscle strength of the trunk the patient’s arms were placed in different positions offering various levels of resistance, as described in Table 2; See also Kendall (20) for further details. To measure strength in trunk flexion in a safe manner, the examiner stabilized the head and neck during curl up for participants with neck flexion score below MRC grade 3. Details about grading are presented in Table 2.

**Walking capacity** – Walking capacity was measured by using the 6MWT according to the American Thoracic Society (ATS) guidelines on a track in a corridor (21), one exception being the track distance, which in this trial was 20 instead of 30 m. The 6MWT is found feasible and reliable as a measure for walking capacity in DM 1 (22).

**Timed up & go** – Timed Up & Go (23) is used for evaluation of mobility and balance. The time used to rise up from a chair with armrest (0.45 m high), walk three meters, turn, walk back and sit down, was recorded. The patients were instructed to walk in a safe manner. The procedure was done twice, and the second test was recorded. Acceptable test–retest stability are documented in DM1 patients (24).

**Rivermead mobility index** – Rivermead mobility index (25) was used to evaluate overall mobility. This 15 item scale comprises items ranging from the ability to turn in bed to the ability to run. The scale is considered valid and reliable in various populations (26–28), and is recommended for use in DM1 (27).

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Recoding the Medical research council MMT score; from six-point to modified 0–3 scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Six-point ordinal scale</td>
<td>0–3 interval scale</td>
</tr>
<tr>
<td>0 = No muscle contraction</td>
<td>0 = Paralysis</td>
</tr>
<tr>
<td>1 = Flicker or trace of muscle contraction</td>
<td>1 = Severe weakness defined as &gt;50% loss of strength</td>
</tr>
<tr>
<td>2 = Active movement with gravity eliminated</td>
<td>2 = Slight weakness &lt;50% loss of strength</td>
</tr>
<tr>
<td>3 = Reduced power but active movement against gravity</td>
<td>3 = Normal strength</td>
</tr>
<tr>
<td>4 = Reduced power but active movement against gravity and resistance</td>
<td></td>
</tr>
<tr>
<td>5 = Normal power against full resistance</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Grading of muscle strength in trunk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscles</td>
<td>Test position</td>
</tr>
<tr>
<td>Trunk flexors</td>
<td>Supine, legs straight</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>None</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*When hip extensors are impaired, fixation on hips. |
†Resistance by examiner: Hand placed mid back, exerts pressure.
**Solbakken et al.**

**Body mass index** – Height and weight was measured and BMI was calculated for each patient.

**Wechsler abbreviated scale of intelligence** – Wechsler Abbreviated Scale of Intelligence was used for assessment of general cognitive level (IQ).

**Data analyses**

Since the modified 0–3 scale is documented to have properties of an interval scale (11), parametric statistics are used for all analyses of muscle strength. Data are presented with mean, range, percent and standard deviation. Pearson’s r is used for correlation. Two-tailed P values < 0.05 were deemed statistically significant and are reported for the correlations; exact P values are reported unless P < 0.001. Group differences are analysed by Independent sample t-tests; mean difference, confidence interval [CI], degrees of freedom (df) and exact P values are reported for the t-test. Inter-item reliability of constructed sums are calculated with Cronbach’s alpha. All analyses were conducted in IBM SPSS v. 21.

**Results**

**Participants**

Thirty eight genetically confirmed DM1 patients were recruited, 21 men and 17 women. 21 fulfilled the criteria of early adult/juvenile, 15 of classic form and two mild adult form. 35 participants were walking independently, two in need of walking aid (walking frame), and one in need of a wheelchair. No participants fulfilled a diagnosis of intellectual disability. Characteristics of the participants and the results of the measures of mobility and balance are summarized in Table 3. We lack CTG reassessment of one patient due to anxiety of needles. One patient did not fulfill criteria for inclusion in the 6MWT due to the need of a wheelchair. Three patients did not fulfill criteria for inclusion in the TUG, one due to the need of wheelchair, and two due to risk of falls. Two participants did not finish their IQ test due to fatigue.

None of the patients were on symptomatic treatment for myotonia or other medication that could influence their motor skills.

**Skeletal muscle strength**

Figure 1 presents mean muscle strength for each muscle group tested. Neck and trunk flexion scores are the lowest and the only muscles measured within severe weakness, (1.58 and 1.52). Back extension is within slightly weakness (2.22).

The highest modified 0–3 score in this sample is the knee extension, knee flexion, and elbow flexion (2.86, 2.83, and 2.69) all within the area of slight weakness.

Figure 2 show the distribution of impairment within the MRC 0–3 scale, in each muscle group. No individuals in our sample scored 0 (paralysis) in any muscle groups. Severe weakness (modified 0–3 grade 1) in trunk flexion muscles was found in 52.6% of the participants. Participants scored within area of severe weakness in neck flexion, ankle dorsal flexion, back extension, and wrist extension (42.1%, 10.5%, 5.3% and 2.6%). More than half of the sample had normal strength in knee extension, knee flexion, elbow flexion, and hip flexion (86.6%, 81.6%, 71.1% and 63.2%).

To investigate progression of muscle impairments in different parts of the body, skeletal muscle groups were put in three categories: Distal extremity group (DE-mg): dorsal extension wrist, dorsal extension ankle, Proximal extremity group (PE-mg): Hip flexion, knee flexion, knee extension, shoulder abduction, elbow flexion, elbow extension, and trunk muscle group (T-mg): abdominal flexion, back extension, neck flexion. The internal

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N</th>
<th>Mean</th>
<th>SD</th>
<th>Min – Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>38</td>
<td>39</td>
<td>12.4</td>
<td>20–63</td>
</tr>
<tr>
<td>CTG expansion (kb)*</td>
<td>38</td>
<td>1.75</td>
<td>1.39</td>
<td>0.23–5.4</td>
</tr>
<tr>
<td>Duration of disease (years)</td>
<td>38</td>
<td>18.1</td>
<td>9.9</td>
<td>5–42</td>
</tr>
<tr>
<td>IQ</td>
<td>36</td>
<td>92.4</td>
<td>14.8</td>
<td>64–137</td>
</tr>
<tr>
<td>BMI</td>
<td>38</td>
<td>27.7</td>
<td>6.9</td>
<td>17–53</td>
</tr>
<tr>
<td>6MWT (m)</td>
<td>37</td>
<td>382.2</td>
<td>145.5</td>
<td>40–815</td>
</tr>
<tr>
<td>TUG</td>
<td>35</td>
<td>6.7</td>
<td>1.95</td>
<td>3.4–11.0</td>
</tr>
<tr>
<td>RMI</td>
<td>38</td>
<td>13.2</td>
<td>2.71</td>
<td>6–15</td>
</tr>
</tbody>
</table>

*Number of CTG triplets equals kb/3.

![Mean muscle strength MRC 0-3](image)
Involvement of trunk muscles in DM1

Muscle strength varies significantly across some disease duration groups for trunk muscle groups (1 > 2–4; P’s < 0.05) and for proximal muscle groups (1 > 4, 2 > 4; P’s < 0.05). No group difference in DE-mg reached statistical significance. Details are shown in Table S1.

Muscle strength; relation to expansion size, walking capacity, balance, and general mobility

T-mg strength and PE-mg strength was highly correlated with CTG expansion (r = −0.64, P < 0.001 & r = −0.57, P < 0.001), the relation between DE-mg and CTG expansion was (r = −0.40, P = 0.015).

Distance in the 6MWT was highly correlated with all skeletal muscle groups. Highest correlation was found between 6MWT and T-mg (r = 0.67, P < 0.001), and PE-mg (r = 0.62, P < 0.001). DE-mg was related to 6MWT at (r = 0.45, P = 0.005).

TUG was highly correlated with T-mg. (r = −0.58, P < 0.001), less so to DE-mg (r = −0.43, P < 0.001) and not significantly correlated to PE-mg (r = −0.3, P = 0.08).

RMI was correlated with all muscle groups: PE-mg. (r = 0.72, P < 0.001), T-mg. (r = 0.66, P < 0.001), DE-mg. (r = 0.43, P = 0.005).

9/38 were in need of respiration aid (BPAP), these participants had markedly reduced strength in abdominal flexors and back extensors compared to the participants without BPAP. Due to the small BPAP sample, no further analysis was done.

Figure 2. The distribution of MRC 0–3 severity grading in all muscles tested.

Figure 3. The mean MRC 0–3 score in the three body parts across disease duration groups. Disease duration groups are based on time since first DM1 symptom.
Solbakken et al.

Possible confounders

BMI is not related to any of the skeletal muscle groups (T-mg $r = -0.11$, $P = 0.53$, DE-mg $r = -0.09$, $P = 0.58$; PE-mg $r = 0.03$, $P = 0.87$). No gender differences were found in muscle strength (T-mg: mean diff $= 0.16$ CI $[-0.14$ to $0.46]$, $t = 36$, $P = 0.29$; DE-mg: mean diff $= 0.71$ CI $[-0.43$ to $0.29]$, $t = 36$, $P = 0.49$; PE-mg: mean diff $= 0.11$ CI $[-0.08$ to $0.31]$, $t = 1.55$, $P = 0.26$).

Discussion

This is, to our knowledge, the first extensive clinical study on strength in trunk skeletal muscles of patients with DM1. We show that impairment of strength in these muscles are frequent, severe and occur relatively early in the progression of DM1. After 11 years of disease we find severe weakness of trunk muscles. These findings question the established assumption that motor impairment in DM1 progress from distal to proximal in the extremities. Trunk involvement has rarely been discussed in the DM1 literature. An exception from this is observations of spine deformity and general weakness, which implies trunk impairment. But these phenomenon are considered to occur late in the progression of the disease (4).

DM1 myopathy as the mechanism behind trunk impairment is strengthened by the previously reported pathological MRI findings of trunk muscles in 9 of 15 DM1 patients (9). Trunk flexors are known to be influenced by BMI and by pregnancies (20). However, in our study there is no significant correlation between trunk flexor strength and BMI and no gender differences. In general, decreased strength in the back extensors is not expected unless some kind of pathology is present (20). The relation observed between strength in trunk muscle groups and CTG repeat size are also in line with DM1 myopathy being a probable mechanism for the observed trunk muscle impairment.

Walking capacity (6MWT), balance (TUG) and measures of general mobility (RMI) were all highly related to muscle strength in trunk muscles. The relation between trunk strength and functions measured by TUG and RMI are understandable as they include transfer from prone to sitting and standing which involve big movements of the trunk; in walking, the relation to trunk strength is less clear since the lower extremities are the main producers of mobility. However a certain amount of stability is needed for locomotion. The trunk impairments documented may thus be relevant for everyday functioning and for understanding the risk of injuries due to falls reported among DM1 patients (11).

Knowledge about the trunk impairments documented in this study may also be relevant for detection of DM1 patients. A tendency for a relation between impairments in trunk muscles and respiration problems is found in this study. This relation may be of clinical significance and should be investigated further.

Patients with Myotonic Dystrophy type 2 is generally regarded as having more proximal muscle impairments than patients with DM1 (2). A study, comparing strength and functioning of trunk muscles in DM1 and DM2, should be initiated.

In DM1 patients, low back pain has been reported to be a common problem (29). Whether our current findings may be relevant in understanding the mechanisms behind back pain in these patients requires further studies.

The pathophysiology of the impaired trunk function documented should be investigated by MRI. Supplemental EMG studies of axial muscles in DM1 patients could confirm possible myopathic changes.

A limitation of our study is the lack of longitudinal data on progression of impairment. The cross-sectional findings reported may be due to cohort biases. Duration of disease is based on self-reported first symptoms. Such self-reported data are prone to inaccurate recollection. Nevertheless, it is necessary for defining disease duration in this group, since the diagnosis often is delayed.

The lack of equivalent data from grip strength obviously influenced the sum score on distal extremity muscles. This contributes to a higher impairment in trunk muscles than distal extremity muscles in our study. The scores of trunk flexion for individuals with neck flexion below MRC grade 3 may be influenced by the examiners stabilization of the patients head and neck. This may have led to a higher score in our participants.

Additional information about the effect of trunk muscle impairment on everyday function are available in RIM if one quantify the quality of the exercises in question (e.g. the use of auxiliary manoeuvre’s when turning in bed and sitting up). This information should be gathered for future studies.

Our findings in the group of patients described could be due to a particular “Norwegian subtype” of DM1. On the other hand, regarding all other parameters, such as strength in the extremities, mutation size, BMI and walking capacity, our results are in line with findings from other populations (6, 11, 22).
It is important to investigate the effect of targeted physical therapy on trunk muscles in DM1 patients. Strength in trunk muscle groups should be considered an outcome measure in future clinical trials where specific objective outcome measures are demanded (30).

Acknowledgments

The study was supported by the Norwegian Society for Neuromuscular Disorders and financed by the Norwegian Directorate of Health. We thank the Department of Medical Genetics, Haukeland University Hospital for reassessing the CTG repeat level of the participants.

Conflict of interest

The authors report no conflict of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article.

Table S1. Mean muscle strength in all muscles across disease duration groups.

References

MRI of trunk muscles and motor and respiratory function in patients with myotonic dystrophy type 1

Gro Solbakken 1,2*, Bård Bjørnarå 3, Eva Kirkhus 4, Bac Nguyen 4, Gunnar Hansen 1, Jan C. Frich 5 and Kristin Ørstavik 6

Abstract

Background: Myotonic Dystrophy 1 (DM1) causes progressive myopathy of extremity muscles. DM1 may also affect muscles of the trunk. The aim of this study was to investigate fat infiltration and muscle size in trunk muscles in DM1 patients, and in an age and gender matched control group. Further, explore how fat infiltration and degree of atrophy in these muscles are associated with motor and respiratory function in DM1 patients.

Method: We measured fat infiltration and trunk muscle size by MRI in 20 patients with genetically confirmed classic form of DM1, and compared these cases with 20 healthy, age and gender matched controls. In the DM1 group, we investigated correlations between MRI findings and clinical measures of muscle strength, mobility and respiration. We used sum scores for fat infiltration and muscle size in trunk flexors and trunk extensors in the analysis of group differences and correlations.

Results: Significant differences between cases and controls were present for fat infiltration in trunk flexors (\( p = 0.001 \)) and trunk extensors (\( p < 0.001 \)), and for muscle size in trunk flexors (\( p = 0.002 \)) and trunk extensors (\( p = 0.030 \)). Fat infiltration in trunk flexors were significant correlated to back extension strength (\( \rho = -0.523 \), \( p = 0.018 \)), while muscle size in trunk flexors was significantly correlated to trunk flexion strength (\( \rho = 0.506 \), \( p = 0.023 \)). Fat infiltration in trunk flexors was significantly correlated with lower general mobility (\( \rho = -0.628 \), \( p = 0.003 \)), reduced balance (\( \rho = 0.630 \), \( p < 0.003 \)) and forced vital capacity (\( \rho = -0.487 \), \( p = 0.040 \)).

Conclusions: Trunk muscles in DM1 patients had significant higher levels of fat infiltration and reduced muscle size compared to age and gender matched controls. In DM1 patients, fat infiltration was associated with reduced muscle strength, mobility, balance and lung function, while muscle size was associated with reduced muscle strength and lung function. These findings are of importance for clinical management of the disease and could be useful additional outcome measures in future intervention studies.

Keywords: Myotonic dystrophy type 1, MRI, Muscle-size, Fat-infiltration, Trunk-muscles, Respiration, Mobility

Background

Myotonic Dystrophy 1 (DM1) is a progressive autosomal dominant inherited multisystem disorder caused by a CTG nucleotide repeat expansion in the myotonic dystrophy protein kinase (DMPK) gene on chromosome 19. DM1 is one of the most prevalent neuromuscular disorders affecting about one in 8000 [1–4]. The motor impairments in DM1 are assumed to progress from distal to proximal in the extremities. Early involvement of the face and anterior neck muscles are common [2, 5, 6]. Spine deformity and general weakness are anecdotally reported to occur late in DM1 progression [4].

We recently documented early and severe impairment in trunk muscles when measured with manual muscle strength tests (MMT) [7]. The trunk impairment was correlated to lower general mobility, reduced balance and use of Bilevel Positive Airway Pressure (BiPAP). The severity of the impairments and their correlation to the size of the CTG expansion suggested that DM1 could...
cause myopathy in trunk muscles [7]. There is a need for more knowledge about trunk muscle impairment in DM1 and how trunk muscle weakening may influence function [8]. Falls are prevalent in DM1 patients, and knowledge of whether myopathy in trunk muscles are related to mobility or balance, is of clinical importance [9]. Respiratory function may also be impaired [3, 10], and represents the main cause of mortality in the group [11]. The abdominal muscles are important for respiratory function [12] and involvement of trunk muscles may therefore indicate a need for ventilatory support [7].

The MMT, though easy to perform in the clinic, does not specify the cause of the weakness. Muscle biopsies in DM1 patients have shown fat infiltration and type 1 fiber atrophy in affected extremity muscles [2]. MRI has turned out to be a useful non-invasive measure of myopathy in muscular dystrophies [13–15]. The few MRI studies of trunk muscles in DM1 have focused on fat infiltration only [13, 14, 16]. The need for atrophy measures in future MRI studies of muscular dystrophies was recently addressed in a review of muscle MRIs [6]. Muscle size measured by MRI is highly related to strength measured by MMT and quantitative handheld dynamometers [17]. Significant correlation between strength and muscle size has also been found in an animal model of DM1 [18]. Edema is previously documented in a large number of DM1 patients in the extremity muscles as well as the erector spinae [13, 14]. Further, edema is found both in muscles with and without fat infiltration or atrophy, and is suggested to precede fat infiltration [14]. To describe muscle involvement in trunk muscles in DM1, we investigated edema as well as fat infiltration and atrophy.

Fat infiltration of muscles has been studied in healthy subjects and is related to age, gender and BMI [19, 20]. These variables are therefore to consider when interpreting MRI findings in DM1 patients. No previous MRI study of trunk muscles in DM1 has compared patients with healthy controls. The aim of this study was to investigate muscle size (diameter and area) and fat infiltration in trunk muscles in DM1 patients, and compare the results to an age and gender matched control group. In the DM1 patients we also aimed to explore whether the amount of fat and the size of the trunk muscles correlate to trunk muscle strength, respiratory function and other motor measurements.

Methods

Recruitment and inclusion
This study is part of a larger observational study on patients with DM1 classic form (defined as disease onset after 10 years): “Myotonic Dystrophy type 1. Mechanisms, course of progression and optimization of development”, focusing on CTG repeats, somatic and cognitive symptoms and pain. The first publication was published in 2016 [7]. A total of 50 DM1 patients have been recruited from different parts of Norway. In the present MRI study, patients living in the region where MRI was performed and without contraindications such as pacemaker or other metal implants, were included. In total, 22 patients were invited and from September 2016 until June 2017, 20 patients who consented to participate in the MRI study were included. 20 healthy age and gender-matched controls were recruited through written announcements to employees at the hospital departments. The invitation to participate as a control was not restricted to employees. Participants were included consecutively, there were no drop-outs after consent.

Disease duration and CTG
In patients, disease duration was calculated based on time between onset of typical DM1 symptoms such as myotonia, loss of strength, cataract or arrhythmia and the date of the MRI investigation. Southern blot analysis [1] for number of CTG repeats was obtained from all patients within three years from the time of the MRI procedure.

Evaluation of motor function

Skeletal muscle strength
MMT was used for assessing strength in the trunk flexors; measured by the curl up, and strength in the trunk extensors; measured by trunk extension from prone (see Additional file 1: Table S2 for procedures) in both controls and DM1 patients at the time of the MRI [21]. Muscle strength was scored with an adapted 0–3 Medical Research Council (MRC) scoring, from MRC 0–5, see Table 1. The ordinary MRC 0–5 scale (Additional file 1: Table S2) has been criticized for its unequal categorical width, providing only ordinal data, and for low discrimination between categories when used in clinical practice [22–24]. To counteract these limitations, the MRC 0–5 scale was recoded to a modified 0–3 scale (Table 1), according to Vanhoutte et al. [24]. By Rasch modelling of strength measure data from 1065 patients with different neuromuscular disorders (including DM1), Vanhoutte et al. documented reliability and restored thresholds enabling the modified 0–3 scale to be analyzed as an interval scale [24].

Evaluation of function in the DM1 group only
Rivermead Mobility Index (RMI) is a questionnaire that measures general mobility. RMI consists of 15 items. The sum range is 0–15. A high sum indicates better mobility performance. RMI is found reliable and valid and recommended for DM1 patients [25, 26] and was measured in the patient group only.

Timed Up & Go (TUG) expressed in seconds, is used for evaluation of mobility and balance. The time used to
rise up from a chair with armrest (0.45 m high), walk three meters, turn, walk back and sit down, was recorded. The patients were instructed to walk in a safe manner, and as fast as possible. The procedure was done twice, and the second test was recorded. Acceptable test-retest stability has been documented in DM1 patients [27, 28]. TUG was only measured in the patient group.

Walking capacity, expressed in meters, was measured by using the Six Minute Walk Test (6MWT) according to the American Thoracic Society (ATS) guidelines on a track in a corridor [29], one exception being the track distance, which in this trial was 20 instead of 30 m. The 6MWT is proven to be feasible and reliable as a measure for walking capacity in DM1 [30] and was measured only in the patient group.

Forced Vital Capacity (FVC) [31], expressed in % of predicted values was recorded from chart information for the patients who had completed this examination of respiratory function as part of their follow up programs in the local hospitals.

Other measurements

Body Mass Index (BMI) [32] expressed in kg/m² was calculated for all persons included, both cases and controls.

MRI measurements, interpretation and scoring

MRI was completed in 20 DM1 patients and 20 controls. MR imaging was performed using 1.5 T. MR unit (Magnetom Avanto, Siemens, Erlangen, Germany) with phased array body coils. The trunk muscles, from the 11th thoracic vertebra level to the level of the lesser trochanter of the hip, were examined by 1): a transversal T1-weighted turbo spin echo sequence performed in two steps with breath holding (TE/TR 9/350 ms; echo train length 3; slice thickness 5 mm; distance factor 200%; field of view (FOV) 370 mm; matrix size 320 × 320; in-plane resolution 1.2mm²; number of slices 15; parallel imaging GRAPPA 2. Total scanning time was approximately 15 min.

The MRI scans were scored independently by two radiologists, with 20 years of experience within the musculoskeletal field. They were aware of age and gender but blinded for clinical information. The images were anonymized, and scored randomly, the readers were blinded for each other's scorings and whether the images belonged to patients or controls. The rectus abdominis -, the abdominal oblique -, the abdominal transverse -, the erector spinae -, the psoas - and the gluteus maximus muscles were scored. Muscle fat infiltration and muscle size were assessed on transversal T1-weighted images at preselected standardized levels that were identified with the help of the sagittal T1 weighted images. Fat-infiltration was scored according to the Mercuri-score, developed for use in muscular dystrophy, and widely used in reporting muscle fat-infiltration in myopathic muscles [33, 34]. The global degree of muscle fat infiltration (grade 0: no fat-infiltration; grade 1: fatty streaks; grade 2: less than 30% fat infiltration; grade 3: more than 30% but less than 60% fat infiltration; grade 4: more than 60% fat infiltration; grade 5: totally replaced by fat) was scored [35]. Grade 0 and 1 were defined as normal. The rectus abdominis muscles were scored in two intervals, above and below umbilicus. The erector spinae muscles were scored in three intervals: (above the L2/L3 disc level; between the L2/L3 and the L4/L5 disc level; and below the L4/L5 disc level. The maximal thicknesses (mm) of the rectus abdominis muscles, the external and the internal abdominal oblique muscles and the abdominal transverse muscles were registered. The muscles were scored in a level above the umbilicus. The maximal thicknesses of the rectus abdominis muscles were also registered in a level below umbilicus.

The areas (mm²) of the erector spinae muscles were registered in the L1/L2, L3/L4 and L5/S1 disc levels [36]. The areas (mm²) of the psoas muscles were registered in the L4/L5 disc level. The areas of the gluteus maximus muscles were not analyzed.

All muscle sizes were assessed including the areas with fatty degeneration.
Muscle edema, interpreted when there were hyperintensity on TIRM images, was assessed at preselected standardized levels that were identified with the help of the sagittal T1 weighted images. All measurements were done manually (Fig. 1).

**Statistical analysis**

The SPSS 24 (IBM Corporation Armonk, NY, USA) was used for calculations. Normal distributed variables were presented with mean, standard deviation (SD) and range. Non-normal distributed variables were presented with median and range. Assessment of group difference between cases and controls, and between patients with and without edema, was done by Independent sample T-tests and Man-Whitney U test when appropriate. Effect sizes (Cohens $d$) were calculated using the online social science statistics service: [http://www.socscistatistics.com/effectsize/Default3.aspx](http://www.socscistatistics.com/effectsize/Default3.aspx). Cohens $d$ at 0.2 were interpreted as small, 0.5 as medium and > 0.8 as large. Correlations between MRI measures and clinical measures were performed with sum scores for fat infiltration, and muscle size: 1) sum fat infiltration in trunk flexors (both the abdominal recti, the abdominal obliques and the abdominal transversus), 2) sum fat infiltration in trunk extensors (erector spinae L1/L2, L3/L4 and L5/S1), 3) sum muscle size in trunk flexors (both the abdominal recti, the abdominal obliques and the abdominal transversus), 4) sum muscle size in trunk extensors (erector Spinae L1/L2, L3/L4 and L5/S1).

A linear regression model with forced entry method was constructed to explore variables related to pulmonary function. Assumptions for Multiple linear regression was met: Linear relationship between outcome and independent variables, multivariate normality, homoscedasticity and no multi collinearity. P-values were set at two-tailed $< 0.05$, and exact values are reported when $> 0.001$. Bonferroni correction is used for adjustment of several statistical group comparisons. Based on power from previous MRI studies we calculated 40 participants to be sufficient (95% power) for answering the case control question. Interrater variability between the two radiologists reading the MRIs was calculated by interclass correlation (ICC (3.1) two - way mixed, consistency)). Mean ICC was 0.90 (excellent). In light of the high ICC only measures from one of the radiologists are presented in this study. Paired sample t-tests were used for comparison of left vs right side muscle size; Wilcoxon signed-rank test were used for comparison of left vs right side degree of fat infiltration.

**Results**

**Group characteristics**

There were no significant differences in age, gender and BMI between the patients and control group. The DM1 patients had decreased trunk extension and trunk flexion strength compared to healthy controls (Table 2). For information about muscle strength in the extremities and neck in the DM1 group, see Additional file 1: Table S1.

Descriptions for the function measures TUG, 6MWT, RMI and FVC as well as the DM1 characteristics CTG size and disease duration are shown in Table 3. None of the patients were treated with Mexiletine or other specific medication for their myotonia. The range show patients being mildly to severely affected, see Table 3.

**Case-control comparison of fat infiltration measured by MRI**

None of the MRI measures showed significant left/right differences. We therefore only report findings from the right side, see Additional file 1: Table S5. There was a significant difference between cases and controls in the degree of fat infiltration in all muscles measured except for the psoas and the transverse abdominal muscles (Table 4).

For details about relations between muscle fat infiltration and BMI and age see Additional file 1: Table S3.

The degree of fat infiltration varied within the patient group. Some patients had total fat replacement in several muscles while others had normal findings. How the different fat infiltration categories are distributed in the various muscles in the DM1 and the control group is displayed in Figs. 2, 3, 4 and 5.

In the patient group the cranial rectus abdominis was the most severely affected muscle, with 45% of the 3 highest (> 30–100%) fat infiltration categories present.
The second most affected muscle was the erector spinae below L4/L5 with 40% of the three highest categories present. For both the erector spinae and the rectus abdominis, the cranial part of the muscles was most frequently fat infiltrated, displaying a cranial to caudal pattern (Fig. 1). The abdominal transverse had the smallest amount of fat infiltration while the psoas was completely within the normal range in the patient group. In the control group, there were normal values and all had the lowest fat infiltration category (Figs. 2 and 3).

**Case-control comparison of muscle size measured by MRI**

Muscle size was significantly different between the groups for three of the measured muscles: both levels of the rectus abdominis and the erector spinae L5/S1. The differences are large for all these muscles and most prominent for the cranial rectus abdominis. The findings in individual muscles and their group differences are presented in Table 5. For details about muscle size and gender in the two groups see Additional file 1: Table S4.

**Edema**

Edema in trunk muscles was found in nine patients and only one control. Further, edema was present in both trunk flexors and trunk extensors, although not present in the abdominal rectus below the umbilicus and the abdominal external oblique, nor in the erector spinae above L2/L3 or the psoas. Six patients had edema in the trunk flexors (abdominal rectus above the umbilicus: one patient, abdominal oblique internus: two patients, abdominal transverse: three patients), six patients had edema in the trunk extensors (erector spinae between L2/L3-L4/L5: 3 patients, and erector spinae below L4/L5: 3 patients) and one patient had edema in the gluteal maximus. Patients with edema had significant higher levels of fat infiltration in trunk extensors ($p = 0.022$), and significantly lower muscle size in trunk extensors ($p = 0.026$).

**Correlation between, MRIs, CTG size and disease duration**

The disease specific CTG-expansion size was not significantly correlated with any MRI measurements; nor sum scores of fat infiltration or muscle size in the trunk flexors and trunk extensors. Disease duration was related to fat infiltration in the trunk flexors ($\rho = 0.47$, $p = 0.037$) and the gluteal maximus ($\rho = 0.57$, $p = 0.008$).

**Correlation between MRI findings and MMT within the DM1 group**

Fat infiltration and muscle size were both related to muscle strength. The sum score of fat infiltration in the abdominal flexors was related to trunk extension strength. On the other hand, the sum score of muscle size in the abdominal flexors was related to trunk flexion strength (Table 6).

**Correlation between MRI findings and motor and lung function in the DM1 group**

Fat infiltration in the trunk flexors were strongly correlated with the RMI and TUG, but not to the 6 MWT. Both fat infiltration and muscle size in the trunk flexors was significantly correlated to FVC, the strongest correlation was found to muscle size (Table 7). FVC was also correlated to the CTG expansion size ($r = -0.67$, $p = 0.003$). A regression model with muscle size of the cranial rectus abdominis and CTG size as independent variables, and FVC as dependent variable, was calculated, and R square for this model was 0.72, both covariates muscle size ($\beta = 0.562$, $p = 0.001$) and CTG ($\beta = 0.537$, $p = 0.001$) had independent contributions.

**Discussion**

To our knowledge, this is the first study of fat infiltration and muscle size in trunk muscles in DM1 patients.
comparing cases and healthy controls. It is also the first study of trunk muscle involvement measured by MRI in relation to results from clinical testing of strength and other muscle function tests as well as respiratory variables. We found a statistically significant difference in fat infiltration and muscle size between patients and age-matched healthy controls. In addition, we have shown that there are strong relations between MRI findings in the patient group and impairment of both motor performance and respiratory function.

### Differences in fat infiltration and muscle size

Fat infiltration was significantly different between cases and controls for all the measured muscles except for psoas, which seems spared by DM1, a result in line with Park et al. [16]. Our clinical findings are in line with our previous study on a larger group of patients [7], where we found impaired trunk muscle strength and that this was significantly related to mobility and balance. However, in this previous study we did not include MRIs. Our findings of fat infiltration in trunk extensors and trunk flexors in DM1 are also in line with other MRI studies of both trunk muscles and extremity muscles in DM1, and other myopathies [13, 14, 16]. However, we included measures of muscle size and levels of muscles in DM1, not previously investigated by MRI; the middle and cranial parts of the lumbar erector spinae and a cranial and caudal part of the rectus abdominis. The

<table>
<thead>
<tr>
<th>Muscles</th>
<th>DM1 patients</th>
<th>Controls</th>
<th>Difference</th>
<th>p-level</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>Range</td>
<td>Median</td>
<td>Range</td>
</tr>
<tr>
<td>a: Differences in individual muscles. Adjusted p level = 0.005.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cranial rectus abdominis</td>
<td>2</td>
<td>0–5</td>
<td>1</td>
<td>0–2</td>
</tr>
<tr>
<td>Caudal rectus abdominis</td>
<td>2</td>
<td>0–5</td>
<td>1</td>
<td>0–2</td>
</tr>
<tr>
<td>External abdominal oblique</td>
<td>2</td>
<td>0–3</td>
<td>1</td>
<td>0–2</td>
</tr>
<tr>
<td>Internal abdominal oblique</td>
<td>1</td>
<td>0–3</td>
<td>1</td>
<td>0–2</td>
</tr>
<tr>
<td>Transvers abdominal</td>
<td>0</td>
<td>0–2</td>
<td>0</td>
<td>0–0</td>
</tr>
<tr>
<td>Psoas</td>
<td>0</td>
<td>0–1</td>
<td>0</td>
<td>0–1</td>
</tr>
<tr>
<td>Erector spinae above L2/L3</td>
<td>2</td>
<td>1–4</td>
<td>1</td>
<td>0–2</td>
</tr>
<tr>
<td>Erector spinae L2/3-L4/5</td>
<td>2</td>
<td>1–3</td>
<td>1</td>
<td>0–2</td>
</tr>
<tr>
<td>Erector spinae below L4/L5</td>
<td>2</td>
<td>1–5</td>
<td>1</td>
<td>0–2</td>
</tr>
<tr>
<td>Gluteus maximus</td>
<td>1</td>
<td>0–3</td>
<td>1</td>
<td>0–2</td>
</tr>
<tr>
<td>b: Differences in sum scores of fat infiltration</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sum trunk flexors</td>
<td>9</td>
<td>(0–13)</td>
<td>4</td>
<td>(0–7)</td>
</tr>
<tr>
<td>Sum trunk extensors</td>
<td>6</td>
<td>(3–11)</td>
<td>3</td>
<td>(0–6)</td>
</tr>
</tbody>
</table>

The scores of muscle fat infiltration are according to the Mercuri-score.
severity of fat infiltration found in the trunk muscles, are in line with fat infiltration found in extremity muscles and thus most likely indicates DM1 myopathy [16, 37]. This high degree of fat infiltration in trunk muscles is also found in other muscular dystrophies [6, 13]. The fact that only three muscles showed case control differences in muscle size compared to the case control differences in most muscles when it comes to fat infiltration may indicate a continuum: A certain amount of fat infiltration must be present before muscle size decreases.

Edema
The finding of edema in trunk muscles in nine patients and only one control indicates edema to be part of myopathic changes in trunk muscles in DM1, which is in line with previous findings investigating edema in trunk extensors in this patient group [14]. The fact that edema is found in both trunk flexors and trunk extensors is in line with our experience [7], as well as other studies finding both muscle groups being affected in DM1 patients [13, 16]. Patients with edema had significantly more fat infiltration and atrophy in the trunk extensors, than patients without edema. This may implicate that the processes occurs simultaneous, but still are in line with other studies suggesting edema to be previous to fat infiltration [14].

MRI findings and respiratory and motor function
We find a high and significant correlation between the sum score of muscle size in the trunk flexors and FVC. We think that this finding reflects the importance of the rectus abdominis in forceful expiration [12]. There was also a significant correlation between the sum score of fat infiltration in the trunk flexors and FVC, which is contrary to a previous study [16]. However, muscle size was the most correlated to FVC, and this finding is in line with muscle volume as the most predictive value of strength function [17]. Trunk muscles in DM1 may clearly be fat infiltrated and atrophied, both myopathic changes related to muscle strength and FVC, and should not be neglected in this patient group. Rather, since respiratory function has impact on life expectancy, we...
suggest that trunk muscle strength should be thoroughly assessed in the clinical follow up of these patients.

Fat infiltration in the trunk flexors is correlated to performance on TUG. Stabilization, flexion and rotation of the trunk are involved in TUG and therefore all abdominal muscles are involved in this task. These findings are of importance in the understanding of how balance may be influenced by trunk impairments in the DM1 group and support our previous finding of a relation between strength in trunk muscles and TUG [7]. Bachasson et al. found that the postural stability and gait in DM1 patients was disturbed and related to strength in the distal part of the lower extremities. The authors also argue that changes in pelvic tilt may play a role in gait disturbances in the DM1 group. However, this study did not investigate the trunk muscles [38]. Our findings suggest trunk muscles should be included when postural stability or balance is investigated in the DM1 group. In patients with facioscapulohumoral muscular dystrophy (FSHD) gait function has been shown to be more related to fat infiltration in the trunk muscles than to fat infiltration in the lower extremities [39]. Interestingly, RMI, the measure of general mobility, was significantly related to both fat and size in the abdominal and the back muscles in our patients. This finding is understandable as this test is composed of gross motor movements, some that are dependent on all trunk muscles working against gravity, which demands strength levels above grade 2 (muscle strength score indicating ability to move the body part against gravity). Since RMI involve all trunk muscles, it is possibly more sensitive to change and seems to be able to predict myopathy in trunk muscles.

### Table 5 Diameter and area of trunk muscles in 20 DM1 patients and 20 controls

<table>
<thead>
<tr>
<th>Muscles</th>
<th>DM1 patients</th>
<th>Controls</th>
<th>t</th>
<th>p level</th>
<th>Cohen’s d</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Range</td>
<td>Mean ± SD</td>
<td>Range</td>
<td></td>
</tr>
<tr>
<td>Cranial rectus abdominis, mm</td>
<td>9 ± 2.5</td>
<td>4–14</td>
<td>12.3 ± 2.3</td>
<td>9–19</td>
<td>4.19</td>
</tr>
<tr>
<td>Caudal rectus abdominis, mm</td>
<td>10 ± 4.6</td>
<td>2–17</td>
<td>15.0 ± 3.7</td>
<td>10–27</td>
<td>3.55</td>
</tr>
<tr>
<td>External abdominal oblique, mm</td>
<td>8 ± 2.3</td>
<td>6–14</td>
<td>9.5 ± 2.9</td>
<td>5–15</td>
<td>1.28</td>
</tr>
<tr>
<td>Internal abdominal oblique, mm</td>
<td>8.3 ± 2.8</td>
<td>3–15</td>
<td>9.3 ± 2.0</td>
<td>6–13</td>
<td>1.09</td>
</tr>
<tr>
<td>Abdominal transverse, mm</td>
<td>3.6 ± 1.2</td>
<td>2–6</td>
<td>3.5 ± 1.1</td>
<td>2–6</td>
<td>0.14</td>
</tr>
<tr>
<td>Sum: oblique and transvers, mm</td>
<td>20.4 ± 4.7</td>
<td>14–32</td>
<td>22.3 ± 5.4</td>
<td>15–33</td>
<td>1.15</td>
</tr>
<tr>
<td>Psoas, mm²</td>
<td>1331.0 ± 372.5</td>
<td>752–2151</td>
<td>1436.7 ± 534.6</td>
<td>757–2605</td>
<td>0.73</td>
</tr>
<tr>
<td>Erector spinae L1/L2, mm²</td>
<td>1812.0 ± 433.7</td>
<td>989–2486</td>
<td>2106.0 ± 714.8</td>
<td>1242–3681</td>
<td>1.57</td>
</tr>
<tr>
<td>Erector spinae L3/L4, mm²</td>
<td>2069.3 ± 445.4</td>
<td>1471–3110</td>
<td>2391.2 ± 685.2</td>
<td>1252–4129</td>
<td>1.76</td>
</tr>
<tr>
<td>Erector spinae L5/S1, mm²</td>
<td>705.3 ± 351.7</td>
<td>0–1276</td>
<td>1010.1 ± 286.1</td>
<td>660–1576</td>
<td>3.00</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Muscle size</th>
<th>DM1 patients</th>
<th>Controls</th>
<th>p-level</th>
<th>Cohen’s d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trunk flexors mm</td>
<td>40 (24–56)</td>
<td>50 (35–73)</td>
<td>0.002</td>
<td>1.05</td>
</tr>
<tr>
<td>Trunk extensors mm²</td>
<td>4587 (2727–6707)</td>
<td>5507 (3281–86,389)</td>
<td>0.030</td>
<td>0.71</td>
</tr>
</tbody>
</table>

Millimeter = mm, square millimeter = mm². The table displays the mean score, standard deviation and range, effect sizes d, and t with its p level are reported for each muscle.
However, which strategy a subject uses, when performing the different tasks of RMI is not fixed and allows for compensation such as using the arms to get from a supine to a sitting position. An accurate observation of how the tasks in the RMI are performed by DM1 patients would be of interest, since this may indicate trunk function impairment.

The 6MWT performed by our patients was not significantly related to any of the MRI findings. One explanation may be the low strength needed from the trunk muscles in walking [40]. However, an MRI study that investigated the thoracic levels of the erector spinae in DM1 patients, identified significant relations between these muscles and the 6MWT [16]. This might indicate that the more cranial parts of the paravertebral muscles are the most important trunk muscles for walking.

MRI findings and relation to trunk muscle strength
The correlation between fat infiltration in the trunk flexors and trunk extension may be explained by the opposing role the trunk flexors have to trunk extensors and the need for co-contraction of antagonists in stabilizing the spine [41, 42]. A lack of correlation between trunk extension strength and fat infiltration in the trunk extensors, may be due to the higher frequency of fat infiltration present in the cranial parts, which were not included in this study, and to a greater demand of power from this part of the erector spinae in the trunk extension test performed [43]. The only significant correlation of muscle size and strength was between the trunk flexors and trunk flexion strength, measured by the curl up, a result in line with muscle volume as the most predictive value of strength function [17]. Compensation from other muscles may be the reason for the lack of relations between muscle size and trunk extension. Only the lumbar part of the erector spinae was included in this MRI study, and both the thoracic parts of the erector spinae as well as cervical extensors and other trunk extensors are known to contribute in trunk extension [44].

MRI and CTG expansion size
CTG expansion size was not significantly correlated with any MRI measure; nor fat infiltration or muscle size, in neither trunk flexors or trunk extensors. This result may be due to the mosaic expression of CTG repeats in different tissues in DM1 patients; a higher number of CTG repeats are found in skeletal muscles compared to blood [45]. A significant correlation between MRI measured fat infiltration in trunk flexors and CTG repeats measured in blood is documented by Park. However, in the same study a correlation between fat infiltration in trunk extensors was not significant [16]. This finding may be taken into account when standards of care are recommended. Health professionals should be aware that decreased respiratory function probably might develop early and independent of CTG size.

Strengths and limitations
This study of well characterised and matched case-control groups was sufficiently powered for the main question of differences in findings between cases and controls. However, it might be that the question of muscle size would have profited on a larger sample.

Table 6 Correlations between MRI findings and MMT 0–3 in the DM1 patient group

<table>
<thead>
<tr>
<th>MRI findings</th>
<th>Muscle strength</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Trunk Extension</td>
</tr>
<tr>
<td>Sum fat in trunk flexors</td>
<td>rho -0.523*, p = 0.018</td>
</tr>
<tr>
<td>Sum muscle size in trunk flexors</td>
<td>r = 0.219, p = 0.353</td>
</tr>
<tr>
<td>Sum fat in trunk extensors</td>
<td>rho -0.427, p = 0.060</td>
</tr>
<tr>
<td>Sum muscle size in trunk extensors</td>
<td>r = 0.140, p = 0.556</td>
</tr>
</tbody>
</table>

*Spearman’s rho for correlations to muscle strength. Fat infiltration is scored according to the Mercuri-score, muscle size is measured in millimeters for trunk flexors and millimeters² for trunk extensors

Table 7 Correlations between MRI findings and function

| MRI measures  | Respiratory function | Motor function | |
|---------------|----------------------|----------------|
|               | FVC n18              | TUG            | RMI | 6MWT          |
| Sum fat in trunk flexors | -0.487* p = 0.040    | 0.630* p = 0.003 | -0.628**p = 0.003 | -0.404p = 0.077 |
| Sum muscle size in trunk flexors | 0.551* p = 0.018 | -0.259p = 0.270 | 0.447*p = 0.048 | 0.377p = 0.102 |
| Sum fat in trunk extensors | -0.220 p = 0.380 | 0.305 p = 0.191 | -0.407 p = 0.075 | -0.12 p = 0.960 |
| Sum muscle size in trunk extensors | 0.349 p = 0.156 | -0.009p = 0.987 | 0.401p = 0.079 | 0.124p = 0.604 |

*Spearman’s rho for fat infiltration, and Pearson’s r for muscle size. Fat infiltration is scored according to the Mercuri-score, muscle size is measured in millimeters for trunk flexors and millimeters² for trunk extensors
Correlations between MRI derived measures and disease specific measures in the DM1 group are underpowered (n = 20). DM1 patients with pacemakers were excluded, and our results might therefore not be generalized to the whole group of DM1 patients. On the other hand, the correlations we have identified may be stronger in a group where symptoms could be more severe, such as patients with pacemakers [46]. A strength of the present study is our optimized MRI protocol, reaching acceptable examination time and especially breath-holding times for this patient group. T1 Dixon sequences may have given us more exact qualitative data [47, 48], but would have prolonged the examination time for the patients. We therefore found it not suitable for the present study and patient population. Another strength of this study is the two experienced radiologists analyzing the MRIs and reaching a mean ICC score of 0.90.

Conclusion
The presence of fat infiltration and atrophy in trunk muscles in patients with DM1 shows that these muscles are affected by DM1 myopathy. Fat infiltration was correlated with reduced balance, and both fat infiltration and increased atrophy was correlated with reduced respiratory function. These findings are of importance for clinical management of the disease and could be useful as an additional outcome measure in future intervention studies.

Additional file

Additional file 1: Table S1. Characteristics of the DM1 groups: muscle strength (Adapted MMT 0–3) in extremity muscle groups and neck flexion. Table S2. Grading of muscle strength in trunk according to Medical Research Council (MRC) 0–5 scale for MMT. Table S3. Correlation between the MRI measures and age and BMI in patients and controls. Table S4. Group differences for muscle size between genders in the 20 DM1 patients and 20 controls. Table S5. Differences between left and right side in individual muscles. (DOCX 20 kb)

Abbreviations
6MWT: Six-minute walk test; BIPAP: Bilevel positive airway pressure; BMI: Body mass index; CTG: Cytosine thymine guanine trinucleotide repeat; DM1: Myotonic dystrophy type 1; DMPK: Myotonic dystrophy protein kinase gene; FVC: Forced vital capacity; MMT: Manual muscle strength tests; MRC: Medical research council; MRI: Magnetic resonance imaging; RMI: Rivermead mobility index; SPSS: Statistical package for the social sciences; TUG: Timed up & go

Acknowledgements
We acknowledge the assistance from Department of Diagnostic Imaging at Drammen Hospital, Vester Viken Health Trust, Department of molecular genetics at Haukeland University Hospital, and Division of Radiology and Nuclear Medicine at Oslo University Hospital.

Authors’ contributions
Conceived and designed the study: GS, BB, BN, EK, JF, KØ. Performed the study: GS, BB, GH, BN, EK. Analyzed the data: GS, BB, EK, KØ. Interpreted the data: GS, BB, GH, EK, KØ. Wrote the paper: GS, BB, EK, BN, GH, JF, KØ. All authors read and approved the final manuscript.

Funding
This work was supported by the Foundation of Sophies Minde and Vester Viken Health trust. The authors have no conflict of interest and have no financial disclosures.

Availability of data and materials
The datasets generated and/or analysed during the current study are not publicly available due to the consent form used, some limitation of data sharing may apply, but are available from the corresponding author on reasonable request.

Ethics approval and consent to participate
This study was approved by the Regional Committees for Medical and Health Research Ethics, South East (reference number 2015/2354). All participants gave their written informed consent.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests. The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author details
1Department of Neurology, Rheumatology and Rehabilitation, Drammen Hospital, Vester Viken Hospital Trust, P.O. Box 800, 3004 Drammen, Norway. 2Department of Clinical Medicine University of Oslo, P.O. Box 1171 Blindern, 0318 Oslo, Norway. 3Department of Diagnostic Imaging, Drammen Hospital, Vester Viken Hospital Trust, P.O. Box 800, 3004 Drammen, Norway. 4Division of Radiology and Nuclear Medicine, Oslo University Hospital, Rikshospitalet, Oslo, P.O. Box 4950 Nydalen, N-0424, Oslo, Norway. 5Faculty of Medicine, University of Oslo, P.O. Box 1130 Blindern, 0318 Oslo, Oslo, Norway. 6Department of Neurology, Section for Rare Neuromuscular Disorders, Oslo University Hospital, Oslo, P.O. Box 4950 Nydalen, N-0424 Oslo, Norway.

Received: 11 February 2019 Accepted: 6 June 2019
Published online: 19 June 2019

References


Publisher’s Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.
Background: Pain is prevalent in myotonic dystrophy 1 (DM1). This study investigated whether CTG repeat size, disease duration, BMI and motor and psychological function were related to pain in adult patients with DM1, and if there were gender differences regarding intensity and location of pain.

Method: Cross-sectional design. Pain was investigated in 50 genetically confirmed DM1 patients by combining clinical assessment and self-reports of pain intensity and locations. Pain scoring results were related to CTG size, disease duration, muscle strength, walking capacity measured by 6-min walk test, activity of daily life by Katz ADL Index, respiratory function by Forced Vital Capacity and BMI. In addition, the degree of reported pain was related to Quality of life measured by WHOQOL-BREF; fatigue was measured by Fatigue severity scale; psychological functions were measured by Beck Depression Inventory, Beck Anxiety Inventory, IQ and Autism spectrum Quotient.

Results: Pain was reported in 84% of the patients and was significantly correlated with CTG size ($r = 0.28$ $p = 0.050$), disease duration ($r = 0.38$ $p = 0.007$), quality of life ($r = -0.37$ $p = 0.009$), fatigue ($r = 0.33$ $p = 0.02$) and forced vital capacity ($r = -0.51$, $p = 0.005$). Significant gender differences, with higher scores for females, were documented. In male subjects the number of pain locations was significantly correlated with quality of life and the autism quotient. In females, pain intensity was significantly correlated with activity, respiratory function and BMI.

Conclusions: Pain in DM1 was prevalent, with a strong association to lung function and other aspects of the disease. Significant gender differences were present for pain intensity and number of pain locations. How pain was related to other symptoms differed between male and female subjects. Our findings highlight the importance of assessments of pain in DM1 patients.

Keywords: Myotonic Dystrophy1, Pain, Gender, CTG size, Fatigue, Quality of life, motor function, BMI, FVC, psychological function, Autism quotient
In this cross-sectional study of adult patients with DM1, we investigated gender differences regarding intensity and location of pain, and whether the degree of CTG expansion, disease duration, motor and psychological function were related to pain.

Participants and methods

Recruitment and inclusion

Adult patients with DM1 from two different regions in Norway were invited to participate in a large cross-sectional, clinical study [15, 16]. The congenital and childhood forms of DM1 were not included, due to their different clinical symptoms [17]. The inclusion period was between 2012 and 2017. Patients were contacted through their respective hospitals, the National registry of neuromuscular diseases and the Norwegian patient organization. Fifty-five patients with a genetically verified diagnosis and a typical history of adult form of DM1, were invited to participate. Of these, 50 patients accepted.

All patients underwent a neurological examination with focus on motor function, and all the data included in this paper were collected during the outpatient visits.

Disease measures: disease duration and CTG size

Disease duration was defined as time between onset of typical symptoms of DM1, which included myotonia, cataract, motor impairment or arrhythmia, and study enrollment [4]. Southern blot analysis for CTG size [1] was obtained from 49 patients at the time of inclusion.

Pain measures

Patients were instructed to mark and score the intensity of chronic pain, which was defined as pain, excluding headache, that had been present for at least 3 months. Pain locations were identified using “pain drawings” (Fig. 1) and the number of pain sites was added up from these drawings [18]. Pain intensity was scored by the subjects as the experienced mean pain intensity based on the numeric rating scale (NRS 0–10): no pain = 0, mild pain = 1–3, moderate pain = 4–6, severe pain = 7–10 [18].

Descriptions of pain quality, which included aching, deep, burning, lancinating or electrical shock, were collected during history taking. Use of analgesics, physiotherapy or other pain management strategies, as well as perceived effect of these strategies, were documented.

Functional measures and questionnaires

Muscle strength was assessed by the Medical Research Councils (MRC) manual muscle strength test (MMT) 0–5 [19]. The MRC MMT 0–5 has been criticized for its unequal categorical width, providing only ordinal data, and for low discrimination between categories when used in clinical practice [20, 21]. To counteract these limitations, we used the MRC 0–3 scale, which has been recoded from the MRC 0–5 scale according to Vanhoutte et al. [22]. The mean of muscle strength was used in all analyses and it composed of the muscle strength in distal extremities (comprising wrist extensors and dorsal flexors of the ankle), proximal extremities (comprising shoulder abductors, elbow flexors, elbow extensors, and hip flexors, knee flexors, knee extensors), and trunk (comprising the trunk flexors/abdominals and the back extensors). Due to previously reported symmetry, only one side was tested [23]. The disease specific Muscular impairment rating scale MIRS [24] was used to investigate the severity of the muscular impairment. MIRS is a 5-point scale where 1 is no muscular impairment, 2 is minimal signs, 3 distal weakness, 4 proximal weakness and 5 severe proximal weakness. The MIRS is reliable and has been validated, though Mathieu et al. advise caution when interpreting small samples due to low interrater reliability [24].

The six-minute walk test (6MWT) was conducted according to the American Thoracic Society guidelines [25]. However, the corridor track in the present study was 20 m long instead of 30 [26, 27]. Mean 6-min walking distance (6MWD) for healthy men between 20 and 50 years is 638 ± 44 m. Mean 6MWD for healthy women is 593 ± 57 m. These values are dependent on age and BMI in healthy populations [26]. Percent-predicted value
for the 6MWD was calculated using reference equations as described by Enright et al.: men: $1.140m - (5.61 \times BMI) - (6.94 \times age)$, women: $1.017m - (6.24 \times BMI) - (5.83 \times age) = [28]$

The Katz Index of Independence in Activities of Daily Living was assessed by interview, to evaluate personal independence in activity of daily living [29, 30]. Forced Vital Capacity (FVC) values [31] and information on possible co-morbidities such as diabetes and thyroid dysfunction and symptomatic medication for myotonia were collected from the patients’ medical files. The fatigue severity scale (FSS) was used to measure general fatigue [32–35]. Scores > 5 on FSS are regarded as high levels of fatigue [32]. Height and weight were measured and body mass index (BMI) [36] was calculated.

Cognitive measures and psychological questionnaires

General cognitive function (IQ) was assessed with the Wechsler Adult Intelligence Scale (WASI II) [37]. Symptoms of anxiety and depression were assessed with the Beck Anxiety Inventory (BAI) [38] and the Beck Depression Inventory (BDI) [39]. The Autism Spectrum Quotient (AQ) [40] was used for assessing the amount of ASD symptoms. And finally, for quality of life, the WHO quality of life-BREF (WHOQOL-BREF) questionnaire was utilized [41].

Statistics

The SPSS 25 (IBM Corporation Armonk, NY, USA) was used for calculations. Normally distributed variables were presented with mean, standard deviation (SD) and range. Non-normally distributed variables were presented with median and range. Assessments of group differences were performed with students t-tests and Mann Whitney u test when appropriate. Effect sizes (Cohens d) were calculated using the online social science statistics service: http://www.soscistatistics.com/effectsize/Default3.aspx.

Correlations were performed with parametric and nonparametric tests when normal distributions were not present. P-values were set at two tailed $= < 0.05$, and Bonferroni corrections were used for adjustments of multiple comparisons for the question of gender differences regarding pain intensity measured by NRS and number of pain locations (NPL). Exact $p$-values were reported when between 0.05–0.001. All analyses of the pain measures and other disease characteristics are descriptive correlations, and not Bonferroni corrected due to their explorative nature. In order to control for group differences in CTG between men and women, a linear regression model with forced entry method was done for NRS, AQ, FVC and 6MWT. Assumptions for linear regression were met. We calculated 50 patients to be sufficient for 90% power to answer the questions of gender differences in pain.

Fig. 1 Pain-distribution (%), all participants
Table 1 Characteristics of 50 patients with DM1

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Mean, SD, (Range)</th>
<th>Men (n 24)</th>
<th>Women (n 26)</th>
<th>Difference between men and women/Cohens d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>40.1, SD: 12.6 (19–63)</td>
<td>37, SD: 13.8 (19–63)</td>
<td>43, SD: 10.7 (23–62)</td>
<td>ns</td>
</tr>
<tr>
<td>CTG kb N49</td>
<td>1.8, SD: 1.4 (0.230–5.4)</td>
<td>1.3, SD: 1.1 (0.270–4.7) n24</td>
<td>2.3, SD: 1.5 (0.230–5.4) n25</td>
<td>P = 0.008/0.8</td>
</tr>
<tr>
<td>Disease duration, years</td>
<td>19.0, SD: 10.0 (5–42)</td>
<td>16.4, SD: 9.6 (5–42)</td>
<td>21.5, SD: 9.7 (6–40)</td>
<td>ns</td>
</tr>
<tr>
<td>Mean strength of trunk muscles (MTT 0–3)</td>
<td>1.7, SD: 0.5 (1–2.6)</td>
<td>1.8, SD: 0.5 (1–2.6)</td>
<td>1.6, SD: 0.4 (1–2.3)</td>
<td>ns</td>
</tr>
<tr>
<td>Mean strength of distal extremity (MTT 0–3)</td>
<td>2.3, SD: 0.5 (1.5–3)</td>
<td>2.3, SD: 0.5 (1.5–3)</td>
<td>2.3, SD: 0.5 (1.5–3)</td>
<td>ns</td>
</tr>
<tr>
<td>Mean strength of proximal extremity (MTT 0–3)</td>
<td>2.6, SD: 0.3 (2–3)</td>
<td>2.7, SD: 0.3 (2–3)</td>
<td>2.6, SD: 0.3 (2–3)</td>
<td>ns</td>
</tr>
<tr>
<td>Fatigue (FSS) Questionnaire N48</td>
<td>4.8, SD: 1.3 (2–7)</td>
<td>4.5, SD: 1.6 (2–7) n23</td>
<td>4.9, SD: 1.3 (3–7) n25</td>
<td>Ns / 0.33</td>
</tr>
<tr>
<td>Walking test (6MWT) N45</td>
<td>382.4, SD:117.6 (123–615)</td>
<td>417.5, SD:103.4 (123–523) n23</td>
<td>348.8, SD:122.8 (140–615) n22</td>
<td>P = 0.049/0.60</td>
</tr>
<tr>
<td>Katz ADL Questionnaire</td>
<td>[6.0] (3–6)</td>
<td>[5.5] (3–6)</td>
<td>[6.0] (4–6)</td>
<td>ns</td>
</tr>
<tr>
<td>Autism quotient index (AQ) Questionnaire N47</td>
<td>17.0, SD: 6.1 (6–32)</td>
<td>19.4, SD: 5.4 (11–32) n21</td>
<td>15.0, SD: 6.1 (6–28) n 26</td>
<td>P = 0.014 / 0.75</td>
</tr>
<tr>
<td>IQ N41</td>
<td>92.0, SD: 14.2 (64–137)</td>
<td>92.5, SD:17 (64–137) n20</td>
<td>91.5, SD: 11.4 (71–114) n21</td>
<td>Ns/ 0.06</td>
</tr>
<tr>
<td>Anxiety (BAI) Questionnaire N43</td>
<td>[4.0] (0–26)</td>
<td>[3.0] (0–26) n22</td>
<td>[4.5] (0–23) n 22</td>
<td>ns</td>
</tr>
<tr>
<td>Depression (BDI) Questionnaire N44</td>
<td>[8.0] (0–37)</td>
<td>[7.0] (0–19) n21</td>
<td>[8.0] (0–37) n 23</td>
<td>ns</td>
</tr>
<tr>
<td>Respiration spirometry (FVC%) N 29</td>
<td>71.7, SD: 18.8 (25–103)</td>
<td>76.4, SD: 14.0 (55–103) n13</td>
<td>67.9, SD: 21.6 (25–91) n16</td>
<td>Ns/ 0.77</td>
</tr>
<tr>
<td>Quality of life (WHO QOL BREF) Questionnaire</td>
<td>89.7, SD: 13.3 (59–115)</td>
<td>91.3, SD: 12.4 (71–115) n24</td>
<td>88.2, SD:14.1 (59–114) n26</td>
<td>Ns/ 0.23</td>
</tr>
<tr>
<td>BMI</td>
<td>26.6, SD: 6.6 (15–53)</td>
<td>26.3, SD: 5.5 (15–34)</td>
<td>26.9, SD: 7.5 (17–53)</td>
<td>Ns/0.09</td>
</tr>
</tbody>
</table>

Mean, [Median] SD, (min/max) are presented. Exact p-values are given for differences < 0.05 between men and women and the Cohens d effect size is reported. DM1 Myotonic Dystrophy type 1, CTG Cytosine, Thymine, Guanine, MMT Manual Muscle strength test, FSS Fatigue Severity Scale, 6MWT Six-minute walk test, Katz ADL Assessment of Activities of Daily Living, IQ Intelligence quotient, BAI Becks Anxiety Inventory, BDI Becks Depression Inventory, FVC Forced Vital Capacity, WHOQOL BREF World health Organization Quality of Life Assessment, BMI Body mass index
measure. All patients completed the pain measures. Details of muscle impairment severity are summarized in Table 2.

The functions measured did not differ between male and female patients. Neither did BMI. However, some Cohen’s d effect sizes are > 0.5, which may indicate group differences for 6MWT, FVC and AQ in a larger group. A possible contribution of CTG size compared to gender for FVC, AQ and 6MWT was investigated using linear regression models including gender and CTG as independent variables, see Table 1. The models show that CTG had a stronger contribution than gender to FVC and 6MWT, whilst for AQ, gender had a stronger contribution compared to CTG (R: 0.34, p = 0.066, Beta CTG = -0.068, p = 0.67. Beta Gender = 0.31, p = 0.053).

Pain

Frequency, intensity and locations

Chronic pain was reported in 84% of the patients, and 32% of these reported severe pain (NRS 7–10). Mean pain intensity was moderate (NRS = 4.6), and the mean number of pain locations (NPL) was 3.2. For gender differences, see Table 3. Pain locations were widespread and symmetrically distributed. The most frequently reported pain locations were the lumbar and cervical parts of the spine and the palmar sides of the hands (Fig. 1).

Pain qualities

Different pain qualities were described. Most of the patients reporting pain described it as aching or deep or both (62%). 22% reported a burning or lancinating pain quality in their feet, distal part of their legs and hands.

Analgesics, physiotherapy and other pain intervention

Of the 42 patients reporting pain, 16 (38%) used analgesic. The following medication was used: Paracetamol was used by 11 patients (26%), four used opioids (9%), Gabapentin was used by three persons (7%), cannabinoids were used by three persons (7%), antidepressants by one person (2%). Five (12%) patients were on more than one type of analgesic.

Seventeen (40%) of the patients reporting pain used physiotherapy consisting of exercise, musculoskeletal mobilization and massage. Acupuncture and manipulation were also used as symptomatic treatment. Of these, 6 patients (14%) combined analgesics and physiotherapy.

All patients experienced some pain relief, while 5 (12%) reported very good pain relief.

Pain correlated to CTG size, age, disease duration and somatic and psychological symptoms

Pain intensity was significantly correlated to CTG size (r = 0.28, p = 0.050), disease duration (r = 0.38, p = 0.007), quality of life (r = -0.37, p = 0.009) and fatigue (r = 0.33, p = 0.02). The number of pain locations was correlated to disease duration (r = 0.36, p = 0.01) and quality of life (r = -0.33, p = 0.01). No significant correlation between the pain measures and age, anxiety, depression, the autism quotient, IQ, muscle strength, MIRS, 6MWT, Katz ADL or BMI were found. The only significant correlation between pain and function measures was between NRS and FVC which were negatively correlated (r = -0.51, p = 0.005).

Pain differences in men and women

Pain frequency

Chronic pain was reported in 71% of the men and 96% of the women. Moderate pain was present in 46% of women and 25% of men, and the percentage of women reporting severe pain was more than twice that in men (42% vs. 20, see Fig. 2).

The distribution of pain locations differed between men and women. However, only pain in the back was significantly more frequent in women. 88% of the women reported back pain compared to 50% of the men (Fisher’s exact test p = 0.005).

Pain intensity and number of pain locations

NRS, as well as NPL were significantly different in men and women (Table 3).

In order to control for the group difference between gender in CTG size, one linear regression was conducted with NRS as a dependent variable. CTG size and gender were independent variables: R = 0.45, p = 0.003, only gender had an independent contribution: β: 0.39, p = 0.008.

Table 2 MIRS distribution

<table>
<thead>
<tr>
<th>MIRS</th>
<th>MIRS mean</th>
<th>MIRS 1</th>
<th>MIRS 2</th>
<th>MIRS 3</th>
<th>MIRS 4</th>
<th>MIRS 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>N 50</td>
<td>3.1, SD:1.1(1–5)</td>
<td>4%</td>
<td>30%</td>
<td>24%</td>
<td>34%</td>
<td>8%</td>
</tr>
<tr>
<td>Men n 24</td>
<td>3, SD:1.1(1–5)</td>
<td>8.3% (n2)</td>
<td>29.2% (n7)</td>
<td>25% (n6)</td>
<td>29.2% (n7)</td>
<td>8.3% (n2)</td>
</tr>
<tr>
<td>Women n 26</td>
<td>3.2, SD: 1 (2–5)</td>
<td>0</td>
<td>30.8% (n8)</td>
<td>23% (n6)</td>
<td>38.5% (n10)</td>
<td>7.7% (n2)</td>
</tr>
</tbody>
</table>

Mean, SD, and range are reported for the total MIRS in the whole group and in men and women. Distribution to the different MIRS categories, is presented as number and percentage of patients for the whole sample and for men and women.

MIRS Muscular impairment rating scale.
Correlations between pain, CTG size, disease duration and symptoms in men and women

The correlation between NRS and disease duration was significant, but only in the female group (rho 0.41, \( p = 0.40 \)). Furthermore, pain was related to different symptoms and findings in men compared to women, see Table 4.

In male subjects, NPL was significantly correlated to quality of life and to measures of socio-cognitive function (AQ). In female subjects, NRS was related to motor function measures, Katz ADL, FVC and to BMI. There was no significant association between pain and MMT.

Discussion

In this study we found a high frequency of chronic pain with a mean value of moderate intensity in adult patients with DM1. Furthermore, pain was widespread and symmetrical, with 3.2 as the mean number of pain locations. In our sample of subjects, only NRS was significantly related to size of CTG repeats, FVC and fatigue. However, both NRS and the NPL were significantly correlated to disease duration and quality of life.

A novel finding was that there were gender differences for pain in DM1 patients. Pain was more frequent, had a greater intensity and was more widespread in female compared to male subjects. How pain is correlated to other symptoms also differs. In men, pain was correlated to the autism quotient (AQ), and quality of life (WHO-QOL-BREF). In women, pain was related to disease duration, activity (Katz ADL), respiratory function (FVC) and BMI.

Table 3 Mean pain intensity and number of pain locations in the whole group and in men and women

<table>
<thead>
<tr>
<th>Pain measures</th>
<th>Whole group N=50</th>
<th>Men (n=24)</th>
<th>Women (n=26)</th>
<th>Difference between men and women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean NRS</td>
<td>4.6, SD: 2.7 (0–9) [5]</td>
<td>3.2, SD: 2.7 (0–8)</td>
<td>5.8, SD: 2.0 (0–9)</td>
<td>asympt. ( p = 0.001 )</td>
</tr>
<tr>
<td>Mean NPL</td>
<td>3.2, SD: 2.4 (0–8) [3]</td>
<td>2.3, SD: 2.3 (0–6)</td>
<td>4.0, SD: 2.2 (0–8)</td>
<td>asympt. ( p = 0.01 )</td>
</tr>
</tbody>
</table>

Mean, Standard deviation: (SD) and (range) are reported. Pain intensity and number of pain locations are both sig. Different for men and women. Median[3].

Bonferroni correction \( p = 0.01 \).

Frequency, intensity and location

Most (84%) of the patients reported chronic pain, and 35% reported severe pain intensity (7–10 on NRS). This is consistent with findings from previous pain studies of DM1 where frequencies between 60 and 88% are described [6, 9, 14]. This frequency is higher than that which has been reported in general in Scandinavian populations. In Norway, the prevalence of chronic pain is reported to be 24% [42]. A review from Sweden and Denmark documented a prevalence of 16 and 18% respectively in non-cancer populations [43]. DM1 affects many organs and most patients can be characterized as multimorbid. Nociceptive pain may likely be present and caused by DM1 myopathy, where muscle tissue over time is replaced by fat infiltration, which leads to loss of function and strength [16, 44–46]. An additional cause may be neuropathic pain, since polyneuropathy is documented in DM1 groups without comorbidity like diabetes or thyroid dysfunction [12]. The quality descriptions of pain may differ in neuropathic compared to nociceptive pain. Pain quality may therefore, to a certain extent, differentiate causes of pain. 22% of the patients with pain in this study reported burning or lancinating pain, possibly indicating neuropathic pain.

The high number of pain locations documented in this study possibly reflects the distribution of muscular affection in DM1 as described in the literature [15, 23]. The most frequent pain locations reported by our patients were the lower back, the neck and the ventral side of the hands. Chronic low back pain is frequent in several populations [47]. Our findings indicate that chronic low back pain is even more frequent among adult DM1 patients than in mixed populations, an observation which was also documented in a study by Miro and co-authors [8, 47]. This might be caused by the trunk muscle impairments in DM1, which also includes severe atrophy of the lower erector spinae muscles [15, 16, 44, 45, 48]. This atrophy may not only cause loss of strength, but also impair co-contraction and muscle recruitment, and may lead to decreased stability of the trunk. Trunk stability is a prerequisite for mobility and for protecting the spine and extremities against injuries and possible pain [49]. In DM1, low back pain may be related to mechanical impairment and thereby nociceptive pain mechanisms such as increased weight on joints and the remaining skeletal muscle tissue.
In addition, weakness of the neck muscles, leading to inability to lift the head from a supine position, is a core clinical feature in DM1 [4]. Neck muscle atrophy may lead to problems with stabilizing the head and neck, thereby causing pain. Hand pain could be explained by the well-known myopathy in distal extremities in DM1 [4]. Indeed, in one case report, the patients’ presenting symptom of DM1 was pain in the hands [50].

### Pain, DM1 duration and CTG

Pain intensity was related to CTG size and disease duration. DM1 is a progressive disorder, and the severity of the disease depends to a high degree on the number of CTG repeats, which probably explains this finding [51]. Peric et al. also found that pain intensity was related to disease duration [14]. During progression of DM1, CTG levels increase, several organs and tissues may become affected, muscle strength decreases and motor and respiratory impairments increase [4]. As muscle strength decreases, activities of daily life become more challenging and possibly demand muscle activity closer to the maximal strength and endurance of the individual patients. Jensen et al. investigated pain intensity in groups with different mobility limitations. They found that pain intensity was significantly higher in DM1 patients with the most impaired mobility, in need of assistive devises for mobility, such as canes, a wheelchair or another person [6]. Pain in another neuromuscular disorder, congenital myopathy, is may be triggered by ADL activities [52]. Furthermore, because muscle work is dependent upon lung function, respiratory deficit may impair motor function even more. Also, in a study of DM1 mice, peripheral nerve affection was found to be related to CTG size [53]. Neuropathy may influence muscle function, both strength, endurance and timing may become impaired [54]. It is therefore possible that the impact DM1 progression and high levels of CTG repeats have on different organs, may lead to pain.

### Pain and anxiety, depression, fatigue and QoL

In contrast to the findings in previous studies on neuromuscular disorders, including DM1, we found no significant correlations between pain measures and anxiety or depression measured by BAI and BDI. This could be due to differences in study design, patient populations and measures [6, 7]. However, several findings in our study imply that pain has an impact on how patients feel and think. Both quality of life and the degree of fatigue were related to pain. Our documentation of an association between pain and fatigue is in line with studies in other patient populations [55]. Fatigue is also related to disease duration in DM1 [9, 56]. In addition, pain is shown to be predictive of fatigue in a longitudinal study on DM1 [57]. The relationship between pain and quality of life in DM1 is in line with findings in other neuromuscular disorders [8, 14, 58].

### Pain and gender

Gender differences in pain are well documented in general populations, with women being more frequently affected [42, 59]. We now document the same phenomenon in DM1. Female DM1 patients report a higher intensity and number of pain locations than male patients. The frequency of pain located in the lower back is also significantly higher in DM1 women. This may be related to the DM1 myopathy leading to lower muscle strength in women compared to men [16, 51]. Others have pointed out that the myopathy in DM1 mimics what is seen in sarcopenia [60]. In the elderly, a certain loss of muscle mass (sarcopenia) is related to chronic low back pain [61]. However, an association between chronic low back pain and the cross-sectional area of muscles is not clearly documented in healthy populations, whereas an association between pain and disability has been [62].

Interestingly, BMI did not differ in men and women. However, BMI was only related to pain in women. That pain is related to BMI is well documented in general populations, and mechanical impairments, as well as

<table>
<thead>
<tr>
<th>Measures</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality of life / WHO QOL-BREF</td>
<td>NRS / Pain Intensity: ρ = -0.51; p = 0.012</td>
<td>NRS/Pain Intensity: ns</td>
</tr>
<tr>
<td>Autism spectrum / AQ</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Respiration / FVC</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>ADL Katz</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>BMI</td>
<td>ns</td>
<td>ns</td>
</tr>
</tbody>
</table>

**Table 4** Correlations between pain and measures of function and quality of life in men and women

<table>
<thead>
<tr>
<th>Measures</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality of life / WHO QOL-BREF</td>
<td>Number of pain locations: ρ = 0.47; p = 0.03</td>
<td>Number of pain locations: ns</td>
</tr>
<tr>
<td>Autism spectrum / AQ</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Respiration / FVC</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>ADL Katz</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>BMI</td>
<td>ns</td>
<td>ns</td>
</tr>
</tbody>
</table>

Exact p-values are reported when ≤ 0.05
ns not significant = p > 0.05
ρ for Spearman’s correlation
inflammation caused by the presence of adipose tissue are suggested as possible mechanisms for this [63]. In DM1, muscles become atrophied and replaced by fat infiltration, and muscle size is significantly smaller in female as compared to male patients [16]. One could speculate that inflammatory mechanisms, as well as mechanical causes may play a role in explaining the gender differences in DM1 patients.

The relation between pain and activity measured by Katz ADL seen in women might be explained by the lower level of muscle strength in DM1 women [51]. A relationship between pain and the most affected muscular regions is reported in FSHD [58]. However, we did not find an association between muscle strength and pain. This may be caused by the MMT measures not being sensitive enough for detecting smaller changes in muscle strength. Another explanation may be that DM1 women report higher pain intensity than DM1 men. Pain intensity > 4 on the Visual Analogue Scale is, to a lesser degree, related to activity [64]. The Katz ADL is composed of physical activity involving flexion, rotation and extension of the spine as well as gross and fine motor movements, which may be avoided to prevent or minimize pain.

We find lower levels of FVC in women than men, and a significant correlation between pain and FVC in women. This could be caused by women having a more restrictive respiratory pattern compared to men. The low FVC seen in women may be influenced by DM1 myopathy in the trunk muscles [16, 51]. Trunk muscles are important in respiration, and the rectus abdominus especially for forced expiration [16, 65]. Severe impairment of the cranial abdominal rectus has been documented in DM1 by our study group, as well as others [16, 44, 45]. FVC may thus be a predictor of a myopathic and impaired rectus muscles function, leading to pain. The relation between lung function and pain may also be caused by hypoventilation. Hypoventilation increases the probability of fatigue and reduced muscle endurance [66, 67].

The association between men’s pain and quality of life has previously been reported in a study on patients with chronic pain [68]. Given the same degree of chronic pain in male and female patients, that study also reported a significantly lower quality of life in men than in women [68]. This relationship may therefore be a general gender difference and not specific for DM1.

For the first time, a relation between symptoms of autism spectrum disease (ASD) and pain in DM1 is investigated. In previous pain studies on individuals diagnosed with autism, both hypo- and hypersensitivity are reported [69, 70]. Whether the correlation between pain and ASD symptoms identified in the current study are due to a common cause, or a result of abnormal self-reporting in individuals with high rates of ASD symptoms, is not known. It is possible that male patients become more attentive to their pain to the degree that it affects or impairs their social communicative function. However, the relationship observed may also reflect a particular disease trajectory in men where ASD symptoms co-occur with pain. Social communicative function such as ASD has been shown to be related to both neurophysiological and structural CNS abnormalities in DM1 [71, 72]. Another study on symptoms in DM1 found higher levels of CNS symptoms in male patients compared to female [13]. This might be in line with the latter explanation, but the relation between pain and social communicative function needs to be further explored in DM1.

Men and women differed significantly in CTG triplet size, and this could contribute to the gender differences in reported pain. However, in the regression model including CTG size and gender, only gender had a significant contribution. This strengthens the conclusion that there is a gender difference regarding pain in DM1, and that we as clinicians have to approach this symptom differently dependent on the sex of the patient.

**Strength and limitations**

The main strength of our study is that we combine subjective and objective measures, in a well-defined patient group with genetic verification of the diagnosis for all participants. Another strength is that the clinical examination and measurements of the CTG size were both performed at the time of the pain assessments. Furthermore, patients were included in a broad assessment study and therefore probably not biased towards participating in a pain study only. This may have strengthened the study’s external validity to the general DM1 adult population. In addition, for the main question of gender differences, the sample size is large enough to make conclusions. A limitation is the cross-sectional design which does not allow for conclusions regarding which directions the relations go. Furthermore, caution must be made for some of the conclusions, given the explorative nature of some of the questions. And finally, since pain is subjectively measured by NRS and NPL, we cannot exclude gender differences in reporting style. We did not use a validated pain questionnaire like Brief Pain Inventory. This should be done in future studies investigating gender differences and pain in DM1. However, both the pain drawing and our measurement of pain intensity are the same as were used in BPI. The difference in CTG expansion size between men and women in our population represents a bias in our sample. Why the included women have more CTG repeats than men is not known, but may be due to the fact that mortality is higher in
more severely affected DM1 men compared to women [13]. Another reason may be that DM1 men are more isolated and might therefore lack the personal support needed to respond to such an invitation [13].

Conclusion

Pain in adult forms of DM1 is frequent and widespread. Mean pain intensity is moderate. Furthermore, pain is related to respiration, disease duration, quality of life, fatigue and CTG size. Pain in DM1 is influenced by gender and significant gender differences are present for pain intensity and number of pain locations. How pain is related to function is also different between men and women. In women, pain seems to be primarily related to respiration, BMI and motor function, while in men pain is more associated with psychological functioning.

Our findings highlight the importance of assessments of pain in DM1 patients, and associated symptoms. These gender-dependent relations between pain and function are important, and should be investigated in future research.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12883-021-02124-9.

Additional file 1: Table 1. Regression models controlling for CTG size and gender.

Acknowledgements

We thank Torodd Hagen MD, and Gunnar Hansen MD, for facilitating this project, expert assistance and medical examinations of the participants.

Conflict of interest

The authors state no conflict of interest.

Authors’ contributions

GS, ED, and KØ conceived and designed the study. GS and KØ analysed the data. All authors interpreted the data, reviewed the manuscript and proved the final manuscript.

Funding

This study was supported by the Sophies Minde Foundation and Vestre Viken Health Trust.

Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due to the consent form used, some limitation of data sharing may apply, but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the Regional Committee for Medical and Health Research Ethics (REC), South East of Norway (REK 2011/2196). All patients gave their written informed consent to participate.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author details

1Institute of Clinical Medicine, University of Oslo, Oslo, Norway. 2Department of Neurology, Rheumatology and Rehabilitation, Drammen Hospital, Vestre Viken Health Trust, Drammen, Norway. 3Department of Clinical Medicine, The Arctic University of Norway, Troms, Norway. 4Section of Clinical Neurophysiology, University Hospital of North Norway, Tromsø, Norway. 5K.G. Jebsen Center for Neurodevelopmental Disorders, Institute of Clinical Medicine, University of Oslo, Oslo, Norway. 6Neurology, Department of Rare Disorders, Oslo University Hospital, Oslo, Norway. 7Institute of Health and Society, University of Oslo, Oslo, Norway. 8Department of Neurology, Oslo University Hospital, Oslo, Norway.

Received: 30 October 2020 Accepted: 16 February 2021
Published online: 04 March 2021

References


Publisher’s Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.