

Force, falls and fear of falls in myotonic dystrophy type 1

Cross-sectional and longitudinal studies

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Cover illustration: Cataratas do Iguçu (Iguazu falls) by Christopher Lindberg, 2005.

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TO ELIA
AND EVERYONE WHO FEELS INCLUDED
IN THE CONCEPT
"MY FAMILY"

POEMS ARE MADE BY FOOLS LIKE ME,
BUT ONLY GOD CAN MAKE A TREE.

Joyce Kilmer (1886-1918).

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ABSTRACT

Background: Myotonic dystrophy type 1 (DM1) is a neuromuscular multi-systemic disorder with slowly progressive muscle weakness. The overall purpose of this thesis was, in adult patients with DM1, to investigate factors of importance for functional balance skills and falls, and to investigate the natural course of muscle force and functional balance impairments, with reliable measurement methods.

Methods: In the first study we evaluated test-retest reliability in static and dynamic balance tests and gait, with three assessment occasions spaced one-week apart, in ten patients with DM1. In the second study, which is a cross-sectional study, 51 patients were assessed for muscle strength, gait and functional balance together with self-reported balance confidence, walking ability and falls. A multivariate analysis of factors of importance for functional balance impairment was performed. Of these 51 patients, 43 were further analysed in a third five-year prospective study for changes in muscle force, gait and functional balance together with self-reported balance confidence, walking ability and falls.

Results: The test-retest reliability analysis results advocate dynamic balance tests and timed gait before the static tests. The cross-sectional study shows that falls are common in the weaker, but still ambulant, patients. A combination of weak ankle muscles and a physical capability to accelerate to fast walking increased the risk of falling. Over five years the distal muscles of the leg have a more steep force decrease than the proximal muscles. There was a tendency towards a greater worsening in males, and we found a statistically significant difference between genders in the knee extensor and flexor force change. All men had fallen within the previous year at the five-

year assessment. Injuries of the face and head were more frequent at five years.

Conclusions: Test-retest reliable dynamic balance tests and isometric muscle force measures showed that there is a statistically significant decrease in functional balance skill and in leg muscle force after five years in patients with DM1. The number of patients who had fallen had increased and the fall injuries were worse. It is of great importance to prevent falls especially in those who are at most risk for falls, by which we mean those who have a more steep muscle force reduction. Regular assessments of gait, functional balance and leg muscle force could be a way to determine who is at most risk for falls. This would give the opportunity to intervene with rehabilitation therapy and assistive devices as possible means for fall prevention in patients with DM1.

Keywords: myotonic dystrophy, physiotherapy, muscle force, postural balance, gait, reliability, cross-sectional, prospective.

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SAMMANFATTNING PÅ SVENSKA

Dystrofia myotonika typ 1 (DM1) är en neuromuskulär sjukdom som inte bara drabbar muskler utan flera organ i kroppen. Trots att DM1 är ovanlig är den ändå den vanligaste muskelsjukdomen bland vuxna, prevalensen är 3-15/100000 invånare.

Denna studie av muskelstyrka, balans, gångförmåga och antal fall inleddes då vi uppmärksammades på de ofta förekommande fallen hos patienter med DM1. En artikel från Skottland visade att antal fall var tiodubbelt högre hos dessa patienter än hos friska. Då våra patienter inte hade berättat om några fall började vi aktivt fråga efter dem, samt undersöka balansförmågan närmare. Vårt syfte med studierna var att, med reliabla balans- och gångtest, undersöka faktorer av betydelse för balansnedsättning och fallfrekvens, samt följa den naturliga utvecklingen av muskelstyrka och balans under fem år. Ett referensmaterial behövde också insamlas.

Inget av de balanstest vi använde hade tidigare utvärderats för patientgruppen. Därför gjordes en studie av tillförlitlighet vid upprepad testning (test-retest) i balanstest under statiska (stillastående) och dynamiska (under rörelse) förhållanden samt gångtest (Studie I). I den andra studien, som var en tvärsnittsstudie, deltog 51 patienter mellan 20 och 60 år. Vi mätte muskelkraft i benen, gång 10 meter, Timed Up&Go (TUG) och Step test (Studie II). Patienterna fyllde även i enkäter om balanstilltro, gångförmåga och fall. Ett referensmaterial inhämtades för gång 10 meter, TUG och Step test utifrån 220 undersökta personer. I den prospektiva studien (Studie III) upprepades undersökningen efter tre och fem år. Fyrtiotre patienter deltog vid åtminstone två tillfällen och räknades in i analysen.

Studie I visade att de dynamiska testen TUG, Step test och gångtest med maximal gånghastighet var mest tillförlitliga efter analys av både absolut variation och relativ reliabilitet.

Studie II visade att det var vanligt med fall även bland våra patienter, samt att muskelstyrka och dynamisk balans var signifikant lägre än de referensvärden för friska individer som vi hade tillgång till respektive samlade in. Faktorer av betydelse för dynamisk balans var muskelkraft i de undersökta benmusklerna, totalt, samt de enskilda benmusklerna var för sig, där fotlyftarna (i 10 meters gång med maximal hastighet, samt Step test) och knäböjarna (i 10 meters gång med självvald hastighet, samt TUG) visade en något starkare korrelation än de mer bálnära musklerna. Faktorer av

betydelse för fallfrekvens var muskelkraft i fotlyftarna och skillnaden mellan tiden att gå 10 meter med snabb eller självvald, bekväm gånghastighet. Även egen tilltro till balans på den aktivitetsspecifika balansskalan (ABC) visade ett starkt samband med fallfrekvens. Risken för frekventa fall ökar med 49% vid varje minskning med 10 poäng på den 100-gradiga skalan.

Studie III visade att muskelstyrkan i samtliga undersökta muskler, hos patienterna med DM1, efter fem år minskade signifikant. Inom gruppen var det stor skillnad på balansfunktionen hos dem som bara var svaga distalt (fotledsmuskler) och dem som var svaga även i mer bål nära muskler (knä- och höftmuskler). Det var också efter fem år en ökande skillnad mellan män och kvinnor; männens kraft minskade signifikant i samtliga muskelgrupper, men hos kvinnorna endast kraften i höftböjarna. Den dynamiska balansen, mätt med TUG och Step test försämrades signifikant hos samtliga. Det gjorde också tilltron till balansen, mätt med ABC-skalan, där 40% av patienterna angav en minskad tilltro med 10 poäng eller mer. Männerna hade en signifikant minskning av tilltron till balansen (medel och median -10.1 punkter, $p=0.04$), men inte kvinnorna. Efter fem år hade andelen patienter som upplevt minst ett fall under senaste året ökat från 58% till 77%, och andelen patienter som behövt uppsöka någon form av vårdinrättning efter fall hade ökat från 16% till 42%.

Att falla när man är muskelsvag kan innebära stora skaderisker, särskilt som förmågan att skydda sig minskar när armmuskulaturen också är svaga. Många patienter hade slagit i ansikte/nacke (en del flera gånger), och olika extremitetsfrakturer förekom. Det finns en risk att man upphör att vara fysiskt och socialt aktiv om man är rädd för att ramla och på fem år ökade andelen som undvek aktiviteter (på grund av rädsla för att falla) från 42% till 60%.

Dessa patienter behöver följas fortlöpande och bör få information, träning samt hjälpmedel. Målet är att patienten i största möjliga utsträckning skall kunna fortsätta vara aktiv utan att drabbas av falloolyckor med risk för skallskador eller arm-/benfrakturer.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

- I. Hammarén E, Ohlsson JA, Lindberg C, Kjellby-Wendt G.
Reliability of static and dynamic balance tests in subjects with myotonic dystrophy type 1.
Adv Physiother 2012; 14: 48–54. With Appendix.

- II. Hammarén E, Kjellby-Wendt G, Kowalski J, Lindberg C.
Factors of importance for dynamic balance impairment and frequency of falls in individuals with myotonic dystrophy type 1 – A cross-sectional study – Including reference values of Timed Up & Go, 10 m walk and step test.
Neuromuscul Disord 2014;24(3)207-15.

- III. Hammarén E, Kjellby-Wendt G, Lindberg C.
Muscle force, balance and falls in muscular impaired individuals with myotonic dystrophy type 1 - A five-year prospective cohort study.
Submitted

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ABBREVIATIONS

6MWT	Six-minute walk test
10mCOM	10 meter walk in comfortable pace
10mMAX	10 meter walk in maximum pace
ABC	Activities-specific balance confidence
BBS	Berg's balance scale
Chi ² , χ^2	Chi squared
CI95%	Confidence interval of 95%
CTG	Cytosine-Thymine-Guanine
CUG	Cytosine-Uracil-Guanine
DM1	Myotonic dystrophy type 1
DMPK	Myotonic dystrophy protein kinase
FES	Falls Efficacy Scale
ICC	Intra-class correlation coefficient
IQR	Interquartile range
MD	Muscular dystrophy
ME	Measurement error
MIRS	Muscular impairment rating scale
MMT	Manual muscle test
NMD	Neuromuscular disorders
OLS	One leg stance

Rho, r_s	Spearman's rho
RNA	Ribonucleic acid
S_w	Within-subject standard deviation
SD	Standard deviation
SEM	Standard error of the measurement
SRD	Smallest real difference
STEP	Step test (according to Hill)
TS	Tandem stance
TUG	Timed Up & Go
Vs.	Versus
WHO	World Health Organization
Y5	Follow-up after five years

DEFINITIONS IN SHORT

Centre of gravity	the vertical projection of the centre of mass (Shumway-Cook and Woollacott, 2007)
Centre of mass	the point that is at the centre of the total body mass, the variable believed to be controlled by the postural control system (Shumway-Cook and Woollacott, 2007)
Dynamic balance	in this thesis defined as postural control <i>in locomotion</i> , in contrast to <i>in still standing</i> (static balance)
Fall	“an event, which results in a person coming to rest inadvertently on the ground or floor or other lower level and other than as a consequence of sustaining a violent blow, loss of consciousness, sudden onset of paralysis as in stroke or an epileptic seizure” (Kellogg, 1987)
Functional balance	the skill of maintaining postural control during locomotion, which is evaluated with performance-based measures of functional balance, see “Dynamic balance” (Shumway-Cook and Woollacott, 2007)
Muscle force	the muscle influence that causes a body part to move or resist movement
Muscle strength	the maximal amount of force exerted in a single attempt (Deschenes, 2004)
Newton	the unit for force. One newton is the amount of force needed to give the mass 1 kilogram an acceleration of 1 m/s^2
Postural control	a complex motor skill derived from the interaction of multiple sensorimotor processes with the two main functional goals of postural orientation and postural equilibrium (Horak, 2006, Shumway-

Cook and Woollacott, 2007)

Static balance

In this thesis defined as postural control *in still standing*, in contrast to *in locomotion* (dynamic balance)

1 INTRODUCTION

For me as a physiotherapist the first encounter with patients who had myotonic dystrophy was unforgettable in many ways. It was not just the odd phenomenon of myotonia in the handshake and the gait pattern with typical slapping forefoot, together with a face marked by muscle wasting; there was something more. Their personality was odd, with dysexecutivity and difficulties in social interaction, typically aggravated by fatigue. These patients had difficulty trusting new caregivers as they had often been misunderstood, and had felt mistreated by and uncomfortable with the common welfare or primary care professionals knowing so little about this neuromuscular disorder. Some caregivers might have seen the patients as learning disabled, and had failed to see the complex symptomatology leading to a correct diagnosis of this hereditary disorder. Some patients denied their problems and defended their belief of normality by all means. At this time a Scottish study was published, showing that stumbles and falls increased tenfold in patients with myotonic dystrophy type 1 compared to healthy controls, with respect to activity level (Wiles et al., 2006). Not a single patient had spontaneously mentioned any frequent falls to us before. Thus, this was a starting point for our studies. After a while, they admitted not only that they had fallen but some also mentioned that, because of their stumbles or their slurred speech, they had not been allowed to visit the local pub or restaurant. Their participation in society at large was therefore limited.

It is worth trying to enable the growth of confidence in patients; the rehabilitation team can really make a difference in these patients' lives. This thesis focuses on the muscle force loss, the falls and fear of falls, and the postural control impairments most patients with DM1 will experience, and the physiotherapy aspects of these functional limitations. There is a lot more to discover.

1.1 Neuromuscular disorders

Weakness, in association with muscle atrophy and decreased muscle tone, is the main characteristic symptom of the neuromuscular disorders (NMD). This stands in contrast to neurological disorders primarily affecting the central nervous system, such as multiple sclerosis and stroke, where the paresis is associated with an increased muscle tone and less pronounced atrophy. The neuromuscular disorders may be acquired or inherited. The

inherited disorders can have different timing with respect to onset, i.e. at birth, during the first year or later in life.

The prevalence of NMD's among adults is approximately 1/1000 (Emery, 1991, Ahlstrom et al., 1993). The NMD's include more than 685 different diagnoses; each of them is rare (Kaplan and Hamroun, 2013). The origin of the inherited NMD's is a genetic defect which in turn affects one part of the motor unit: the alpha motor neuron cell body in the anterior horn of the spinal cord; the peripheral nerve; the endplate; or the muscle fibre itself (Emery, 1991, Kaplan and Hamroun, 2013). The motor neuron diseases, neuropathies and endplate disorders, as well as the acquired muscle disorders, are not the focus of this thesis. The inherited disorders of muscle encompass muscular dystrophies, myopathies and the myotonic disorders. The myotonic disorders are divided in the non-dystrophic disorders, i.e. myotonia congenita Thomsen or Becker and the dystrophic disorders, i.e. myotonic dystrophy type 1 (Steinert, 1909) and 2 (Liquori et al., 2001).

The impairments of patients with neuromuscular disorders are multiplex. Besides impairments related to muscle weakness in some disorders, patients frequently have affected cardiac function, either as conduction defect or heart failure (Bushby et al., 2003), in others the nervous system is affected giving cognitive impairments (D'Angelo and Bresolin, 2006). Impaired hearing or affected vision may be part of some NMD's (DiMauro et al., 1998).

The development of muscle function is complex. In healthy children the muscle force increases with age, as does the motor performance. In patients with muscular dystrophies there is a loss of muscle strength over time leading to impairment of locomotion, upper extremity function and hand grip. In some NMD's loss of strength in bulbar muscles leads to impaired speech, chewing and swallowing (Sonies, 1997). Loss of strength in respiratory muscles may give hypoventilation and/or impaired cough (Wallgren-Pettersson et al., 2004). Loss of strength in core muscles may lead to scoliosis, which sometimes demands surgical intervention (Mullender et al., 2008). A pronounced weakness in the extremities could lead to joint contractures (Vignos, 1983). Muscle pain is related to overuse or disuse of weak muscles in patients with NMD's (Bushby et al., 1998, Abresch et al., 2002).

1.2 Myotonic dystrophy type 1

The most common inherited myopathy among adults is myotonic dystrophy type 1 (DM1; Steinert's disease) (Steinert, 1909). The prevalence in Europe

is approximately 3-15/100 000 (Harper, 2001), but it differs greatly from region to region in the world. It has a high prevalence (189/100 000) in the northeast region of the Quebec province, Canada (Mathieu et al., 1990) and is as rare as 0.9/100 000 inhabitants in Taiwan (Emery, 1991). At the Neuromuscular Centre in Gothenburg, the reference centre for neuromuscular disorders in the Western part of Sweden, the number of known diagnosed adult patients (≥ 18 years) with DM1 was 110 in 2006. The number of adult inhabitants in this part of Sweden was 910 000 this year, which makes the prevalence in the adult population 12/100 000. This lies in the upper part of the European range. In an epidemiologic study in Örebro county 1993, Ahlström found 19 patients with myotonic disorders per 100 000 inhabitants (Ahlstrom et al., 1993).

The gene defect in DM1 is an unstable expansion of CTG trinucleotide repeats in a non-coding region of the myotonic dystrophy protein kinase (DMPK) gene on chromosome 19 (Brook et al., 1992, Fu et al., 1992). Individuals in the general population have less than 35 CTG repeats. A repeat length between 35 and 49 is considered a premutation. A length of 50 CTG triplets or more is pathogenic. There is a rough positive correlation between number of repeats and the severity of the disorder (Salehi et al., 2007) and a negative correlation with age of onset. Patients with the congenital form of DM1 usually have 1000 up to >2000 repeats.

DM1 has an autosomal dominant inheritance, and affects males and females equally. There is a considerable risk of anticipation, i.e. the CTG expansion increases when transmitted to the next generation. This is particularly evident when the mother is the mutation carrier. The child will thus have a markedly increased CTG expansion and a more severe form of DM1 compared to the affected parent (Howeler et al., 1989).

DM1 is a RNA-mediated disease, where the RNA with CUG repeat expansions accumulates in nuclei and impairs splicing of several different genes. This explains why the expanded CTG-repeats in a non-coding region of the DMPK gene can do so much harm in different body structures (Ranum and Cooper, 2006).

The DM1 is a multi-system disorder. Functional disturbances in different organs - the heart, eyes, stomach and brain - are common (Gagnon et al., 2007a, Gagnon et al., 2007b). The organs and tissues most affected in DM1 are those that consist of non-renewing cells, such as the skeletal muscle, the heart and the central nervous system (Melacini et al., 1988, Minnerop et al., 2011) The respiratory system can also be affected, with hypoventilation with

hypercapnea due to weakness of respiratory muscles, while some patients have central and obstructive sleep apnoea (Begin et al., 1983, Yu et al., 2011, Pincherle et al., 2012). Dysphagia is a life-threatening symptom, often evolving later in life (LaDonna et al., 2010). The expected life span of patients with adult-onset DM1 may be shortened, median survival was shown to be 60 years for males and 59 for females (de Die-Smulders et al., 1998). The most frequent primary causes of death, in this register study on 180 adult-onset patients, were pneumonia and cardiac arrhythmias. The definition of adult-onset was age at onset between 10 to 50 years of age, myotonia and progressive weakness, and absence of mental retardation (de Die-Smulders et al., 1998).

The characteristic symptoms, though, are muscle wasting and progressive muscular weakness, typically first noticed in the distal muscles of upper and lower extremities. There is also the myotonic phenomenon, a delayed muscle relaxation, which is due to a reduced chloride conductance (Logigian et al., 2005). The muscular weakness is a progressively disturbing obvious symptom. The myotonic feature can also be disabling, but usually diminishes as the weakness increases. Histopathological findings are marked type I muscle fibre atrophy and central nuclei (Vihola et al., 2003, Angelini and Tasca, 2012). When the genetic mutation was discovered the use of muscle biopsy for diagnosis was terminated and now a blood sample is sufficient to determine a DM1 diagnosis.

At present, there is no cure for patients with inherited neuromuscular diseases including DM1, but the research on gene therapy or protein restitution therapy is on-going. Medical interventions though, have increased life span and improved the quality of life of many patients with NMD's. These interventions can include cardiac and respiratory care, alleviative medication and nutritional support. From the rehabilitation point of view there are different kinds of physical and occupational therapy interventions, including hand exercise programmes (Aldehag et al., 2013) and assistive equipment, as well as individualised exercise programmes focusing on e.g. breathing and coughing techniques (Yeldan et al., 2008); strength (Lindeman et al., 1995, Tollback et al., 1999, Nilsagård and Kånåhols, 2004, Sjogreen et al., 2010); aerobic/physical exercise (Ørngreen et al., 2005, Kierkegaard et al., 2011a); or multidisciplinary rehabilitation programmes (Missaoui et al., 2010).

The patient

The DM1 disorder is classified in relation to the symptom debut as: congenital (0-1 year); childhood (1-10 years); classical/adult (>10 years or early adult); and late onset/mild form (>40 years) (Harper, 2001). A majority

of the individuals with congenital DM1 have a learning disability (Ekström et al., 2009).

The patients in our study had childhood, classical or mild form DM1. The patient with the childhood form often has experienced school difficulties, abdominal problems, clumsiness and indistinct speech (Harper, 2001, Meola and Sansone, 2007). The extremity muscle symptoms are usually not prominent until adolescence or early adulthood. Cardiac conduction abnormalities may be found from 10 years of age (Bassez et al., 2004). The patient with the classical/adult form presents with the typical muscle symptoms myotonia and progressive muscle weakness in adolescence or early adult life. These symptoms start in the distal and facial muscles. The patients may also have excessive daytime sleepiness, irritable bowel syndrome and cardiac rhythm abnormalities (Harper, 2001, Angelini and Tasca, 2012, Laberge et al., 2013). The personality trait may be pathologic, with mostly dependant or harm avoidant personality (Winblad et al., 2005). The patient with the late onset/mild form could present with cataracts in middle age. Muscular symptoms are rare and mild. They are recognised as patients with DM1 in the mapping of relatives with the disorder in order to prevent cardiac arrests.

Another way to classify patients with this disorder is according to the severity of muscular impairment. This classification is named the muscular impairment rating scale, MIRS, elaborated by Mathieu et al (Mathieu et al., 2001). Manual muscle testing of 11 muscle groups bilaterally is the base of the MIRS grading system (see Methods, 3.3 Procedure - Classification for more details).

In the skeletal muscle of a patient with DM1 there is an on-going disease process (Ono et al., 1986). Usually the strength decrease starts in the patient's oral or facial muscles bringing about nasal speech and a myopathic face (facies myopathica) (Mathieu et al., 2001, Sjögren et al., 2007). The myotonia phenomenon is prominent in the early stages of the muscle strength decrease, and shows primarily in the handgrip and the tongue. As the dystrophy proceeds, the patient's handgrip, wrist extensors, neck flexors and ankle dorsiflexors decrease in strength (Harper, 2001, Mathieu et al., 2003). As the muscle strength decreases it will, secondarily, affect the patient's gait pattern and postural control. At the early stage the patient's impairments could be negligible, but when the muscle strength in the feet and shanks weakens further, the patient starts to walk with a foot tap, stumble and eventually, fall (Horlings et al., 2009).

Most of the patients with non-congenital DM1 are ambulant until their 6th decade. Gait velocity, walking distance, walking aids, and stair walking could be important parameters for assessing activity and participation in general life. Progression of muscle weakness is expected (Johnson et al., 1995, Harper et al., 2002, Contardi et al., 2012). Ergonomic interventions as well as physical advice are increasingly important, as many adults with DM1 have a low physical activity level (Lindwall, 2010, Kierkegaard et al., 2011b). Secondary to the muscle weakness, the patient may also complain of an impaired balance resulting in stumbles and falls, often in conjunction with walking (Wiles et al., 2006).

There is a high variability in function and physical impairment between patients with DM1, as well as in cognitive function (Winblad et al., 2006, Gagnon et al., 2008). A common problem in this patient group is the gastrointestinal dysfunction, with e.g. stomach pain and diarrhoea (Harper, 2001). As the DM1 disease is dominantly inherited, patients with DM1 may have children at home with similar or worse impairment (Gagnon et al., 2007b). Their children may be severely learning disabled and/or have an autism spectrum disorder (Ekström et al., 2008). These everyday bodily infirmities, cognitive problems and social situations may also lead to frequent cancellations and loss to follow-up medical appointments or research studies (Tollback et al., 1999, Ørngreen et al., 2005, Gagnon et al., 2007a). Hence, it is important to customise any planned intervention in this patient group.

1.3 Description and evaluation of affected areas of body function

1.3.1 Muscle function

Some aspects of muscle function are power, strength and endurance (Deschenes, 2004). Power is defined as “explosive strength”; strength is “the maximal amount of force exerted in a single attempt”, and muscular endurance is “the capacity to resist muscular fatigue, particularly when the resistance is submaximal” (Deschenes, 2004). In this thesis the only muscle function parameter assessed is muscle strength, defined as the maximal amount of isometric muscle force exerted in a single attempt. Muscle force causes a body part to move or resist movement; force is measured in newton, N.

In healthy individuals muscle strength reaches its peak at about 30 years of age. The more prominent decline normally starts between 50 to 60 years of

age, and there is a more rapid course beyond the age of 60 years (Larsson et al., 1979, Deschenes, 2004). Both men and women exhibit the same rate of muscle strength decrease (Lindle et al., 1997). In healthy adults, during ageing, the skeletal musculature undergoes sarcopenia, the degenerative loss of muscle mass (uppermost the fast type II-fibres), muscle strength and muscle function (Thompson, 2009, Cruz-Jentoft et al., 2010). The rate of sarcopenia in humans older than 50 years is estimated to 1-2% per year (Thompson, 2009). Unlike the histopathologic findings in DM1 patients, the age-related loss occurs preferably in the type II fibres. Later, in senescence, an age-associated hypotrophy is also seen in the type I fibres (Thompson and Brown, 1999).

Evaluation of muscle strength

Common ways to clinically quantify muscle strength are: 1) rough estimation of isometric and dynamic muscle strength against manual resistance; 2) functional muscle strength tests, e.g. counted heel-raising or knee-bowings; 3) manual muscle testing with Medical Research Council scale (MRC, 1978) with positions according to Janda (Janda, 1983); 4) quantitative handheld isometric measurements, with a force gauge dynamometer; and 5) quantitative dynamic muscle strength measurements with e.g. isokinetic/isotonic apparatus.

Rough muscle strength tests and functional muscle strength tests assesses side differences and strength reduction related to the examiners experience and judgment of “normal” strength.

The manual muscle testing is a widely used assessment tool with explicit measurement starting positions and measures strength throughout the range of motion. It aims at giving information on dynamic muscle strength, but is found to be not sensitive enough to be useful in most research studies, even after modifying to more scale steps (Florence et al., 1992, Bohannon, 2005, Gagnon et al., 2013). Nevertheless, it was used in a study of physical profile in patients with DM 1 (Nitz et al., 1999) and in the classification of muscular impairment of patients with DM1, MIRS (Mathieu et al., 2001).

Handheld dynamometry is considered one of the most reliable measurements of isometric muscle force possible to use in the clinical setting. When quantifying moderate muscle strength impairments in DM1 handheld dynamometry has shown advantages over manual muscle testing, and has been recommended for use in patients with neuromuscular disorders (Escolar et al., 2001, Hebert et al., 2010). Reference values of muscle force in newton

are available for both upper and lower extremities (Bäckman et al., 1995, Phillips et al., 2000).

One limitation of all manual muscle testing methods, including handheld dynamometry, is the examiner's own strength and subsequent difficulties with stabilisation, which can occur when testing strong muscles. In some muscle groups "normal" muscle strength could be difficult or impossible to measure with a handheld dynamometer (Bohannon, 1988). In patients with a progressive muscle weakness due to a neuromuscular disorder this is seldom a problem. However, in strong muscles, e.g. in male patients with the mild form of DM1, this has to be taken into account.

The strength measurement method using a handheld dynamometer can be applied either with the "make" or the "break" method (Bohannon, 1988). In both methods the isometric muscle force is generated during 3-4 seconds in a well-described position against a resistance (the dynamometer) at a well-described anatomic landmark. The positions are in most cases neutral to gravity. The difference is the way to end the measurement, holding completely still in the "make" method; or the patients' maximal force effort is overcome by the examiner and the joint gives way, the "break" method (Bäckman et al., 1995, Phillips et al., 2000).

Dynamic muscle strength measurement with computerised isokinetic/isotonic apparatus was not used in this thesis, but it is unlikely that test reliability would have increased in a way that would have changed the possibilities to draw any further conclusions (Bäckman, 1988).

1.3.2 Gait

The ability to walk is a prerequisite for a number of activities and also sometimes for active participation in society, since it gives the able bodied person a greater freedom of choice (Kierkegaard and Tollbäck, 2007). Walking is also recognized as one of the best forms of physical activity for older adults, and great benefits can be gained through regular walking (Morris and Hardman, 1997). Muscle weakness affects the gait through decreasing speed (Busse et al., 2006), changing the gait pattern (D'Angelo et al., 2009, Galli et al., 2012) and increasing the risk of stumbles and falls (Wiles et al., 2006). The gait pattern in patients with DM1 often shows a "foot tap" early as the ankle dorsiflexors (m. tibialis anterior and mm. peronei) weaken, but when the disorder progresses other gait alterations may appear, e.g. hyperextension of the knees if the m. quadriceps wastes away and a shorter step length if the plantar flexors (m. triceps surae) becomes

weak (Fish and Nielsen, 1993). This could all affect the activity level of the patient with the neuromuscular disease DM1 (McDonald, 2002).

Evaluation of gait

Gait can be assessed qualitatively, to evaluate disorder-typical tripping, ataxia or spastic gait patterns; or quantitatively, as speed in meter/second, or the time to walk a specified distance, e.g. 10 or 30 meters (Wade, 1992). Other quantitative gait variables are stride length, step frequency, and cadence. The time to walk a flight of stairs could also be included in the assessment of gait (Wade, 1992). The six-minute walk test has been used in patients with DM1 to evaluate walking capacity and exercise tolerance (Kierkegaard et al., 2011a). Subjectively the patient could estimate the maximum walking distance possible.

Measurements of gait can be performed in many ways, with different kinds of technical equipment. There are “Gait mats” (GaitMat™, GAITRite® etc.), video-analysis and laboratory measures that are examples of technically advanced and expensive tests. Gait *speed* measurement assumes a constant movement, without acceleration (or deceleration). As we wanted to include the sometimes slow start of the DM1 patients, we chose to measure *time* to walk 10 meters (Wade, 1992, Robertson et al., 2006, Graham et al., 2008). Reference values of time to walk 10 meters, in healthy men and women between 20 to 59 years of age, had to our knowledge previously not been published although walking speed (without acceleration and deceleration phases) is thoroughly evaluated (Öberg et al., 1993, Al-Obaidi et al., 2003, Bohannon, 2008). Missaoui et al. have published a study reporting results of a rehabilitation programme with a retrospective analysis, including gait speed in spontaneous and fast condition (Missaoui et al., 2010), but a prospective study of the gait performance in patients with DM1 has not previously been published.

1.3.3 Postural control

The function of maintaining postural stability and equilibrium of the body during static and dynamic conditions is complex. In this thesis the theoretical background to postural control, as it is explained in physiotherapy research, is adopted (Horak, 2006, Shumway-Cook and Woollacott, 2007). A dynamic integration of the sensory (visual, somatosensory and vestibular), musculoskeletal, nervous and cognitive systems is required for postural control. Extrinsic factors as the environment and the task itself, as well as intrinsic factors as personality and biomechanical restraints, influence the resulting performance of the movement tasks (Shumway-Cook and

Woollacott, 2007). The concept of balance is used as a synonym to postural stability which means “the ability to control the centre of mass in relationship to the base of support” (Shumway-Cook and Woollacott, 2007), p.158. Tests that examine the ability to perform functional tasks requiring postural control, in locomotion, are in this thesis named “dynamic balance tests”. Tasks reflecting steady-state postural control are called “static balance tests”.

Static condition

Postural orientation and postural stability are the functional goals of postural control (Shumway-Cook and Woollacott, 2007) p.160. The base of support is crucial in static conditions. Lost postural stability in steady-state demands different strategies to be recovered. They can be named “fixed base of support strategy” vs. “changing base of support strategy”. Sometimes they are simply named ankle, hip or step strategies (Nashner, 1987, Shumway-Cook and Woollacott, 2007) pp.165-169. Normally which muscles activate to maintain equilibrium is a continuum of movements. The use of the fixed base strategy with help from the ankle requires an intact range of motion and a certain amount of muscle strength in the postural muscles of the lower leg, m. soleus, m. gastrocnemius and m. tibialis anterior (Horak, 2006). The individual will as a reflex use this strategy to cope with small perturbations on firm ground. Being unable to counteract the disruptive movement with the lower leg muscles a rapid movement in the hip region (flexion/extension) will be performed. When the *fixed base* strategy is insufficient the individual will take a step to regain equilibrium, i.e. use the *changing base of support* strategy (Nashner, 1987, Horak, 2006, Maki et al., 2008).

Dynamic condition in standing

In dynamic conditions postural adjustments are used in a proactive way, a stabilising of the body precedes a voluntary movement. Anticipatory and feedback control mechanisms are used to adjust forces needed for postural stability (Shumway-Cook and Woollacott, 2007).

Postural control in locomotion

The concept of locomotion requires progression, postural control and adaptation ability. The movement pattern has to be flexible to meet expected and unexpected obstacles, and allow a change of speed if needed. The step length will be reduced when walking on e.g. slippery or icy surfaces (Patla, 1997). The demands on postural control increase when stepping over obstacles (Chou and Draganich, 1997, Hahn and Chou, 2004). Attention processing resources are required in locomotion, the quantity depending on the difficulty of the task (Chen et al., 1993, Maki and McIlroy, 2007).

Dynamic balance tests reflect in part the functional balance skills; e.g. the postural control and adaptation ability in every-day movements.

Many falls occur when turning around. The turning strategies have been studied in healthy, young individuals (Hase and Stein, 1999). The spin-turn and the step-turn strategies were shown. While the latter is stable and easy, having a broad base of support, the spin-turn is the more unstable method.

Evaluation of postural control

As postural control depends on the function in several contributing systems, the test of postural control has to reflect this. The clinical assessments of balance should include tests of several different aspects of postural control (Pollock et al., 2000, Horak, 2006). The assessment should be selected from knowledge and understanding of balance and postural control, and be associated with what the specific individual performs. The different impairments of postural control have induced a development of various assessment tools to assess balance: e.g. the Berg Balance scale (BBS) (Berg, 1989), Functional Reach Test (FRT) (Duncan et al., 1990), Timed Up & Go (TUG) (Podsiadlo and Richardson, 1991), Activities-specific Balance Confidence scale (ABC) (Powell and Myers, 1995), Step test (Hill et al., 1996) and the Balance Evaluation Systems Test (BESTest) (Horak et al., 2009).

The most common still-standing balance tests are: standing on one leg; Romberg's test (feet together, closed eyes) and sharpened Romberg (tandem stance) (Briggs et al., 1989). Open or closed eyes, firm or soft ground, horizontal or tilted surface can vary the postural control demands. Some of these tests are often included in the more complex balance measurement scales (Berg, 1989, Horak et al., 2009). The BBS, TUG and FRT has been used in patients with DM1 (Missaoui et al., 2010).

The performance-based measure of functional balance skills, Timed Up & Go test (Podsiadlo and Richardson, 1991), was developed by Podsiadlo from another measure, "Get Up & Go", in which the quality and fall risk were assessed (Mathias et al., 1986); TUG also included timekeeping. TUG was primarily aimed to assess basic mobility skills in frail elderly persons, but has been further applied in e.g. stroke and vertigo patients and modified for use in children (Whitney et al., 2004, Ng and Hui-Chan, 2005, Williams et al., 2005). TUG has demonstrated ability to distinguish fallers from non-fallers in older people, cut-off has been set to >14 seconds (Andersson et al., 2008). Construct validity was demonstrated as TUG could discriminate between subjects' dependence. All completing TUG in < 20 seconds were

independent in basic transfers. Subjects requiring ≥ 30 seconds were dependent (Podsiadlo and Richardson, 1991). The use of TUG in patients with DM1 has previously not been evaluated for test-retest reliability, and reference values for healthy men 20-59 years of age are not previously established (Bohannon, 2006).

In the Step test by Hill (Hill et al., 1996) the patient does not climb the platform, just place the foot on it and then take it down again, repeatedly, as fast as possible. It aims to assess the ability to maintain balance while performing a fast dynamic single limb stepping task. The original study evaluated the test in relation to two platform heights, 7.5 and 15 cm. The lower height was recommended. Normal values for women 20-80 years of age have been published for the 7.5 cm height (Isles et al., 2004). The test has not previously been evaluated for use in patients with DM1, and further the test lacked reference data for men.

1.3.4 Perceived balance confidence and walking ability

The subjective perception of balance confidence and walking ability are important tools to understand and become aware of the difficulties the patients are experiencing. "Perceived self-efficacy is concerned with judgments of how well one can execute courses of action required to deal with prospective situations" (Bandura, 1982). A high sense of self-efficacy may enhance effective solutions to upcoming postural instability, as well as individuals with a low sense of efficacy may more easily visualize failures and potential falls (Bandura, 1989). Instruments assessing self-efficacy in walking and balance are often used in studies on older people, as falls and decreased balance are more common, and more hazardous, in the elderly. As no earlier studies of perceived balance in patients with DM1 had been performed, we tried to find some well-described, simple and psychometrically analysed questionnaires, with relevant items or activities for the patient with DM1.

Patient reported outcome measures

Two well-renowned questionnaires were the Falls Efficacy Scale (FES) (Tinetti et al., 1990), later modified and translated to the Swedish version, FES(S) (Hellström and Lindmark, 1999); and the Activities-specific Balance Confidence scale (ABC) (Powell and Myers, 1995). Both are developed to study older populations. The FES has been shown to correlate with walking pace, anxiety and depression in the elderly (Tinetti et al., 1990), and both FES and ABC could discriminate between high and low mobility individuals

as defined by perceived need for personal assistance to ambulate outdoors (Powell and Myers, 1995). The FES was more appropriate for assessing balance confidence in more frail seniors. The ABC scale, though, was more adequate to use in more highly functioning (elderly) individuals or individuals at various levels of function, and could more clearly separate the two mobility groups. Both questionnaires have the ability to reflect clinically meaningful changes over time, if used in the proper group (Powell and Myers, 1995).

The self-reported walking index (RW-index) was developed to measure the subjective opinion on current walking difficulty (Bergland et al., 2002, Bergland et al., 2006). The RW-index has its origin in Scandinavia, which could support its feasibility of use in a Swedish population.

1.4 Falls

A fall is defined by WHO as “an event, which results in a person coming to rest inadvertently on the ground or floor or other lower level” (Kellogg, 1987, WHO, 2012). This definition is also used in this thesis. For greater clarity, only falls from standing or walking were asked to be reported.

In October 2012 the World Health Organization’s Media centre published a fact sheet on falls claiming that falls “are the second leading cause of accidental or unintentional injury deaths world wide”. To prevent falls the WHO advises fall-related research and establishing effective policies to reduce risk, together with education, training and creating safer environment (WHO, 2012).

The aims of fall prevention programmes are, according to WHO: reduction of “the number of people who fall; the rate of falls, and the severity of injury should a fall occur”. Further, the WHO is very clear in the description of fall prevention programmes for older individuals, a small section of the advice follows: “muscle strengthening and balance retraining prescribed by a trained health professional; prescription of appropriate assistive devices to address physical and sensory impairments; community-based group programmes which may incorporate fall prevention education and Tai Chi-type exercises or dynamic balance and strength training...”

Tripping and slipping

Research on falls has shown that most falls among older people result from tripping over an object (35-47%) and slipping (27-32%) (Overstall et al., 1977, Gabell and Simons, 1985). Inadequate slip recovery was in a study

shown to depend on a lower rate of muscle activation in the support limb (Tang and Woollacott, 1998). Determinants for recovery from trips have been studied (Shumway-Cook and Woollacott, 2007). It was shown that the hip flexors of the swing leg and the ankle plantar flexors of the stance leg were the most critical muscles for recovery (Chen et al., 1993). Furthermore, the study showed that an even more critical factor than muscle strength appeared to be how fast the restorative forces could be generated. Following experimental induced trips in a lab on a healthy experimental group with 79 participants, age mean (SD) 72.5(5) years, women fell four times more often than men and the younger among the women (65-70 years of age) fell more often than the older (Pavol et al., 1999). The age of the men did not affect the trip outcome, only one man fell, he was >75 years old. The majority of the induced trips did not result in a fall.

Activity restriction associated with fear of falling has shown to be an independent predictor of decline in physical function, in an elderly population (Deshpande et al., 2008).

To follow the WHO intentions, a primary goal is to find out which older individuals are falling, and if it is possible to make assumptions about risk of falling. According to WHO, the fall-related mortality rates (per 100000 population) have the highest numbers in the European region; and in all regions of the world, adults over 70 years (particularly females) have significantly higher fall-related mortality rates than younger people.

Evaluation of number of falls

It is important to have a clear and simple definition of a fall, reliably understood by lay people, to be able to measure number of falls in individuals living at home. The prospective measurement of falls is the preferable method, and is practised in randomised controlled studies using diaries, calendars or postcards. Daily recording is recommended, and ascertainment details about the falls at least monthly (Hauer et al., 2006). A non-published pilot intervention study (at the Neuromuscular Centre in Gothenburg) discovered low compliance while using diaries in patients with DM1 even for a shorter time.

2 AIMS

The overall purpose of this thesis was, in adult patients with DM1, to investigate factors of importance for functional balance skills and falls, and to investigate the natural course of muscle force and functional balance impairments, with reliable measurement methods. In addition, a purpose was to establish reference values in healthy men and women, 20-59 years old for timed 10-meter walk, Step test and Timed Up & Go.

3 METHODS

3.1 Design

All studies are quantitative studies with continuous and categorical data.

Study I is a test-retest reliability study of static and dynamic balance tests including timed 10-m walk.

Study II is a cross-sectional study of functional balance skills, timed 10-m walk, muscle force and self-reported balance confidence, walking ability and falls. Reference data of dynamic balance tests and timed 10-m walk is included.

Study III is a prospective study over five years, with assessments at three occasions of functional balance skills, timed 10-m walk, muscle force and self-reported balance confidence, walking ability and falls.

3.2 Subjects

3.2.1 Patients with DM1

When the studies began the number of genetically proven patients with DM1, living in the western part of Sweden, known and cared for at the Neuromuscular Centre at Sahlgrenska University Hospital in Gothenburg, were 110. Inclusion criteria were age between 20 and 60 years and ability to perform Timed Up & Go. Exclusion criteria were: other disorder interfering with postural control or the congenital form of DM1. Of these 110 were 38 not invited, details on reasons for not being included is shown in Table 1. A dropout analysis of the remaining 72 individuals that were invited is shown in Table 2.

3.2.2 Reference group

In order to establish reference values for dynamic balance tests a healthy reference group was recruited by announcements in different work places; chemical factory, geriatric care, hospital, school and university. The individuals had to assert an absence of balance problems. The goal was to include 20 subjects of each gender and each age-decade between 20-59 years. The tests included walking 10 meters at a comfortable and maximum speed, TUG, and the Step test.

Table 1. Exclusion analysis of patients not invited, number and percent. N=38.

	Excluded by:			
Rationale	Age ^a	Congenital DM1 ^b	Mobility impairment ^c	Other reasons ^d
N (%)	20 (53%) 6/14	9 (24%)	7 (18%)	2 (5%)

^a Bottom row n= <20 years / >60 years.

^b Congenital form due to medical card, or living in a community centre for cognitive impaired.

^c Mobility impairment due to medical card.

^d E.g. communication problem due to other native language.

Table 2. Dropout analysis, number (%).

Invited, N=72			Dropout
Accepted	Declined^a	No answer	Accepted, but dropped out
54 (75%)	14 (19%)	4 (6%)	3 (6%)

^a Transport reasons, “too far to travel”, n=8.

3.3 Procedure

All 72 eligible patients with DM1 were invited by letter and/or by phone call to participate in the studies. Those who agreed to participate (n=51) were examined and made self-assessments at a single visit at the clinic, the cross-sectional study (paper II). Those who agreed to return twice during the following weeks were included in the reliability study and were thus examined at three occasions (paper I). All patients who had participated in the cross-sectional study were invited to the same assessments in the prospective study (paper III), at three and five years after the first visit, Figure 1. The patients were asked to inform the investigator if they were aware of any contributors to postural control impairment other than muscle

Figure 1. Flowchart of the studies

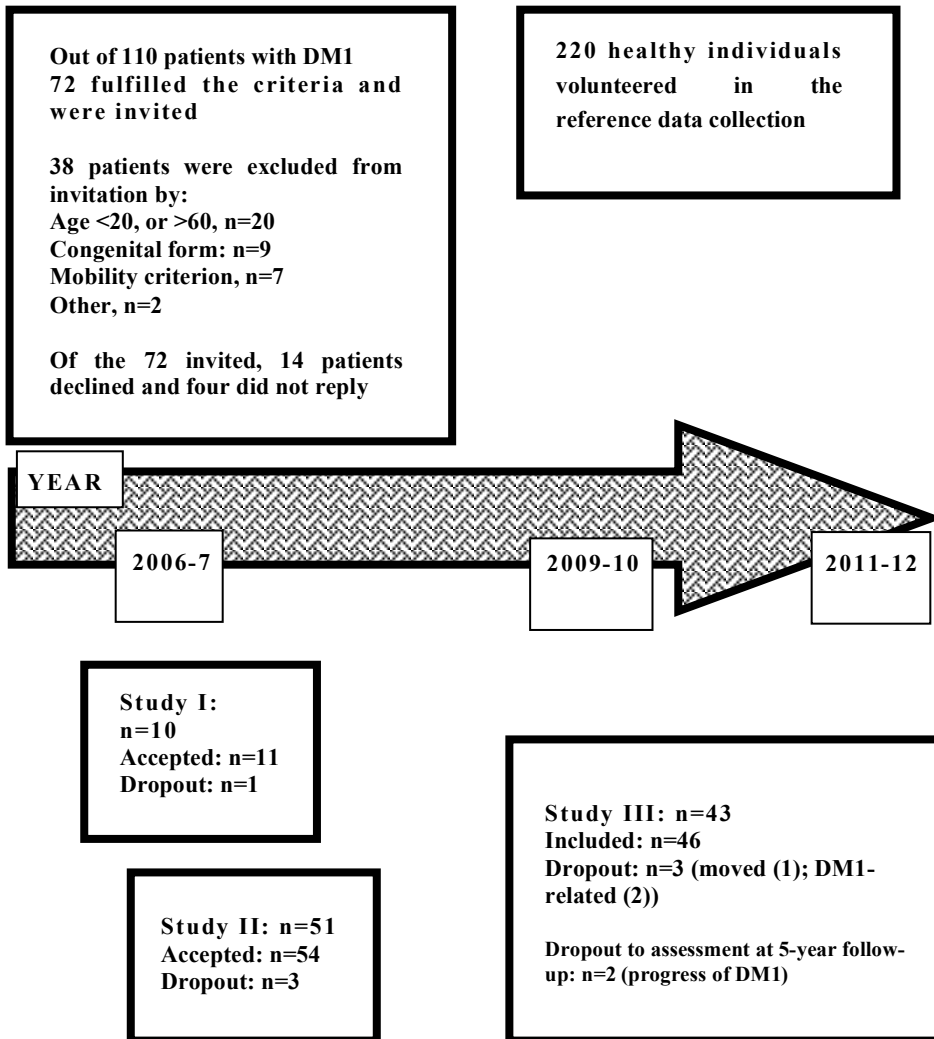


Table 3. Subgroup analysis of 4 individuals, excluded from the prospective study. Data from baseline / follow-up assessment at three or five year.

Excluded patients				
	ID 1	ID 2	ID 3	ID 4
Follow-up occasion	Five year	Three year	Five year	Three year, at a home visit ^a
Years of age/sex	20/female	27/male	53/female	55/female
MIRS, grade	2/2	1/1	1/1	5/5
RWI, grade	12/12	12/12	12/12	6/6
TUG, (seconds)	7.7/7.8	9.5/7.7	8.1/7.7	31.0/56.9
DEX, (newton)	223/270	382/380	277/275	23.2/0

Abbreviations: MIRS, muscular impairment rating scale; RWI, reported walking index; TUG, Timed Up&Go; DEX, Ankle dorsiflexion.

^aWheelchair user outdoors at three year. Deceased after four years, DM1 related.

weakness. The prospective study (paper III) was performed with the same patients as the cross-sectional study, the exclusion criteria were the same, but the inclusion criteria for the analysis were narrower. All patients were followed, but for the analysis the patients needed to have muscular impairment symptoms corresponding to MIRS 3, 4 or 5 (see below, Classification) and be able to perform TUG in less than 30 seconds at their first visit. The reason for the former criterion was that patients with MIRS 1 and 2 have the mild form of DM1, and thus have very little muscle symptoms. The mild form of DM1 is also reasonably stable over time, in our experience. The reason for the TUG criterion was that this cut-off in the elderly distinguishes between individuals dependent or independent in basic transfers; and that patients walking so slowly would in a three years perspective be likely to be a wheelchair user, and need other forms of care and support.

A subgroup analysis shows the characteristics of the excluded patients, Table 3. One patient with slow TUG-time was deceased before the three-year follow-up and is therefore not described in this table.

Classification

MIRS is an ordinal five-point scale developed to assess the progression of the muscular involvement in DM1. Manual muscle testing of 11 muscle groups bilaterally is the base of the MIRS grading system. Patients are thus graded as follows: 1 - no noticeable muscular impairment; 2 - minimal signs, e.g. myotonia, facial weakness and nasality, but no distal weakness except isolated digit flexor weakness; 3 - distal weakness, no proximal weakness except in elbow extensors; 4 - mild to moderate proximal weakness; and 5 - severe proximal weakness, with movement restrictions due to gravity (Mathieu et al., 2001).

Examiners

One experienced physiotherapist assessed all patients with DM1 on all occasions, blinded to previous results. The questionnaires were always filled-in during the first part of the visit in order for the patient not to be affected of the balance tests' results. Resting pauses between the tests were allowed and encouraged.

Three different examiners, one experienced physiotherapist and two physiotherapy students examined the reference group participants. The measurement methods were thoroughly practiced by the examiners to minimize measurement error.

3.4 Measurements and assessments

3.4.1 Muscle force

In study II and III the isometric muscle force was measured, in newton, with a handheld gauge meter (Mecmesin Basic Force Gauge 1000 N, Chauvin Arnoux Group). The measurements were performed in the specific positions outlined by the reference guidelines (Bäckman et al., 1995, Phillips et al., 2000). The knee extensor was assessed in sitting, with 90-degree flexion in the hip and knee; the examiner stabilised herself against a wall. The supine position was used in the hip flexor measurement, the hip in 90-degree flexion, with the knee flexed; and in the ankle dorsiflexor measurement with the distal leg supported on a small wedge pad. The prone position with 90-degree knee flexion was used for the knee flexors. Each muscle was measured three times; the mean of the two highest results was recorded. The

resistance was gradually increased in the gravity neutral position during 3-4 seconds when the patient's maximal muscular force was overcome and the tested joint gave way, the "break method" (Bohannon, 1988). Muscle force was measured in study II and III.

The reliability of handheld dynamometry has shown to be excellent in test-retest with ICC_{2,2} values (using mean values of two measurements) between 0.97-1.00 and a coefficient of variation (CV%) between 3.0%-5.3% in lower limbs (Wang et al., 2002), and in intra-rater reliability with ICC >0.91 in all measured muscle groups (Merlini et al., 2002, Visser et al., 2003). The inter-rater reliability has shown varying results, ICC's from 0.69-0.98, with lower ICC's especially in the strong muscles; i.e. knee extensors (ICC 0.88) and ankle dorsiflexors (ICC 0.69) (Merlini et al., 2002). Reference values of muscle force in newton from two sources were utilised (Bäckman et al., 1995, Phillips et al., 2000).

3.4.2 Timed 10-m walk

10-m COM and 10-m MAX

With a still-standing start the patients walked in a self-selected comfortable speed (10-m COM) and in maximum speed (10-m MAX) a straightforward walk 10 meters in a long corridor with even surface towards a target 2.5 m beyond the 10 m mark. The examiner was standing by the 10 m mark with a stopwatch. At the comfortable speed the timekeeping started as the patients moved forward from the starting point, after the examiner had said "Are you ready? Then you can start walking". At the maximum speed the instructions were to start at the word "Go" (in the starting phrase "Ready-Steady-Go!") and then walk as fast as possible without running or risking stumbling. At the word "Go" the timekeeping started. In both cases the timekeeping ended as the trunk passed the 10 m mark. Hence acceleration was included but not deceleration (Wade et al., 1987, Bohannon, 1997, Watson, 2002, Bohannon and Williams Andrews, 2011).

In the cross-sectional study (paper II) both comfortable and maximum gait speed was measured. As the reliability study (paper I) showed a preference for the maximum gait speed, the comfortable gait speed was abandoned and for that reason not measured at the three and five years assessments (paper III).

3.4.3 Performance-based measures of functional balance skills

Our experience of physical difficulties in patients with DM1 guided our choice of functional balance tests to make it easier to complete as well as the wish of feasibility in all kind of clinical settings, bearing in mind expense and technical aspects (Jarnlo, 2003).

In study I, both static and dynamic balance tests were evaluated for reliability. The tests of postural control, which are not presented below, are described in detail in the Appendix to study I. They were: Standing with feet together, with eyes open; Standing on one leg (right and left), with eyes open and closed; Tandem stance, with eyes open and closed; Walking in a figure-of-eight.

Two performance-based measures of functional balance were, together with the timed walk, after the reliability study (paper I), included in study II and III: the TUG, (Podsiadlo and Richardson, 1991); and the Step test by Hill (Hill et al., 1996).

Timed Up & Go

In the present thesis the TUG was performed in its original manner: from sitting in an armchair (45 cm high) with the hands on the arms of the chair, the patient rose and walked in a comfortable and safe pace to a mark 3 m in front of the armchair, turned, went back and sat down (Podsiadlo and Richardson, 1991). Timekeeping started as the patient's back left the backrest, and ended as the buttocks reached the seat. The TUG was always done twice; the second performance was recorded. Inter-rater, intra-rater and intra-session reliability is high in TUG, with ICC's of 0.90-0.99 (Norén et al., 2001, Steffen et al., 2002, Wang et al., 2009). Smallest real difference was shown to be 1.1 second in community-dwelling elderly (Wang et al., 2009).

Step test

The Step test by Hill was performed with a low block (height 8 cm) as recommended in the original paper (Hill et al., 1996). The starting position was unsupported standing with parallel feet placed 5 cm behind the block (8x40x40 cm). The patient was requested to place the foot fully up onto the block and then return it fully back to the floor as many times as possible in 15 seconds. Any side step or other disruption of the postural control would end the test and in that case only the completed steps up to that point were recorded. Both the right and the left leg were tested, after practice. The Step test has shown relative reliability, ICC >0.90 in healthy older subjects, and

significant correlations with the functional reach test, gait velocity and stride length (Hill et al., 1996). It has also shown high responsiveness, the Standardised response measure (the average change score over a set period of time/SD of that change) showed 0.92-0.95 in hemiplegic patients (Bernhardt et al., 1998).

3.4.4 Patient reported outcome measures

In study II and III the patients filled in questionnaires of balance confidence and walking difficulties as well as answered semi-structured questions on falls. All individuals got support from the examiner with reading, writing and explanation of the questionnaires, if needed.

The Activities-specific Balance Confidence scale

The ABC scale (Powell and Myers, 1995, Myers et al., 1996, Myers et al., 1998) was used to assess the patients' subjective perception of their balance self-efficacy. The scale consists of 16 indoor and outdoor non-hazardous activity items, requiring transferring, bending, reaching or walking. Each item is rated on a 0-100 scale of confidence after the question "How confident are you that you can maintain balance and remain steady, when doing (the specific activity)?" Responses range from no confidence at all (0) to full confidence (100) in maintaining balance. The mean of the 16 items is used as a sum score of balance confidence.

The ABC scale has shown high stability over time ($r=0.92$, $p<0.001$), high internal consistency (Cronbach's alpha 0.96), good scalability (the coefficient of scalability, $H=0.59$, strong cumulative scale) and a good convergent and criterion validity (Powell and Myers, 1995). The ABC has also shown concurrent validity with the SAFE (Survey of Activities and Fear of Falling in the Elderly) worry scale, Pearson's correlation coefficient r showed -0.65 , $p<0.001$, a higher score on worry implied a lower ABC score. A lower ABC score correlated significantly with older age, slower gait speed, lower Berg's Balance Test score, longer TUG time, greater activity restriction, more falls within the previous year, greater number of chronic illnesses and assistive devices (Talley et al., 2008). It has also been used in Sweden in studies with stroke patients and in dizzy patients (Jarlsäter and Mattsson, 2003, Forsberg and Nilsagard, 2013). A healthy elderly population with high mobility had a mean score 80.9 in the original study, whereas the elderly with low mobility scored 68.4 (Powell and Myers, 1995, Myers et al., 1998). We performed a pilot interview study that supported the relevance of the activity items in the patients with DM1.

Self-reported walking index

The RW-index consists of five questions regarding perceived imbalance and difficulties during indoor and outdoor walking, and use of walking aids. The possible scores in three questions are 1 or 2, the other two questions have possible scores 1, 2 or 3. Thus the potential sum score is 5 to 12, where 12 show no subjective walking difficulties, and 5 means large subjective walking difficulties including use of walking aids indoors. When use of walking aids was confirmed, the patients in our study were also asked to report what type of aids they used, e.g. ankle-foot orthoses and walking sticks.

The RW-index has shown concurrent validity with clinical tests and had the highest correlation with comfortable walking speed ($r=0.62$), Timed Up & Go ($r=-0.59$), and walking in a figure of eight ($r=-0.59$) (Bergland et al., 2002). The above mentioned pilot interview study also supported the relevance of the RW-index items in the patients with DM1.

Semi-structured questions on falls

Lastly, the examiner asked semi-structured questions on the occurrence of falls: During the previous year, how many unintentional falls have you experienced? How did it happen? Did the falls result in any injuries? Did you need any medical care? The patients were also asked if they were afraid of falling (yes/no) and if they avoided activities due to fear of falling (yes/no). If so, the activities were defined.

If the number of falls were too many to actually remember, some memory cues were provided to assist the patient in estimating number of falls based on incidents during the last week and month.

3.5 Analysis of the data

Study I

The patients were assessed on three occasions with one week in between. The relative reliability and the absolute variation were estimated. To control for any systematic main effects between the three occasions, an analysis of variance with repeated measures was performed. As a significant main effect was detected a further analysis of the levels was performed.

Study II

Data were analysed for the whole group and divided in subgroups. The whole group was compared with available reference data from a healthy reference

group and from published reference values (Bäckman et al., 1995, Phillips et al., 2000). The division in subgroups were in one part of the analysis patients with MIRS 1-3 and patients with MIRS 4-5; on the other part the group was divided in genders. For estimation of bi-variate correlation between falls and other variables the Spearman's rank correlation was used. The number of falls had a skewed distribution, and therefore the variable was divided into three ordered categories of "fall groups", namely 0-2, 3-6, and ≥ 7 falls per year. Ordinal regression modelling was used to analyse the odds ratio for factors associated with the underlying ordered structure among categories.

Study III

At least two visits per patient were considered necessary to include the patient in the analyses of natural disease course progression. When data was missing at the five-year assessment the missing values were substituted with the values from the three-year assessment, "last value carried forward". The changes were analysed within the whole group (paired data) and for differences between groups (males and females).

3.5.1 Statistical analysis

An expert biostatistician was engaged as a consultant during all parts of the studies.

Mean and standard deviation (SD) and 95% confidence interval (CI 95%) were presented in continuous data; for ordinal or skewed data the non-parametric statistics was applied, median and quartiles (Q1;Q3) or minimum and maximum values. Dichotomous data were presented with number and percent.

To analyse the relative reliability, the intraclass correlation coefficient $ICC_{2,1}$ (two-way repeated measures analysis of variance) was used in study I (Weir, 2005). Measures of absolute variation were estimated using the standard error of the measurement (SEM), the repeatability, and the measurement error (ME) (Bland and Altman, 1996, 1999). To investigate any confounding effects between the three occasions, the analysis of variance (ANOVA) with repeated measures was used together with F -test of significance. If a confounding effect was detected a further analysis of the levels was performed with paired t -tests (paper I). The calculation of smallest real difference (SRD) is algebraically similar to the limits of agreement described by Bland & Altman, also called 'repeatability' (Bland and Altman, 1986). Lastly, in this thesis, $SRD\%$ was calculated by dividing SRD by the mean of the test results, multiplied by 100 (Beckerman et al., 2001).

In study II the differences between groups were analysed with Student's t-test. Bi-variate correlation was estimated using the Spearman's rank correlation coefficient to explore correlations between the number of falls and the other variables: muscle force and functional balance skills; and also between the different dynamic balance tests and muscle force. Ordinal regression was used to analyse the odds ratio for factors associated with the underlying ordered structure among categories. Thus, the falls were divided into three ordered categories "fall groups", which were set to 0-2, 3-6 and ≥ 7 falls last year. The dependent variable "risk of falls" with these three categories was then analysed for factors of importance. First uni-variate, and then multi-variate analyses were performed to find the two most important factors (paper II).

In study III, differences over time between groups in continuous data were analysed: with the Wilcoxon signed rank test for paired data; and the Mann-Whitney U-test for unpaired differences (men and women). For analysis of ordered categorical data or dichotomised variables the Sign test was used for comparisons over time, and Mantel-Haenszel χ^2 Exact test between groups (paper III).

All significance tests were two-sided at the 5% significance level. Calculations were made in SPSS[®], Statistics, up to v20 (IBM, USA) and SAS software, Version 9.

3.6 Ethical approval

According to the Declaration of Helsinki the individuals participated voluntarily after verbal and written information, and a written consent to participate in the study was obtained. The participants knew they could refuse further participation without any impact on further treatment. The Regional Ethical Review Board in Gothenburg, Sweden approved the study (Dnr 248-06 and Dnr 601-11).

4 RESULTS

The baseline characteristics of the patients in each study are shown in Table 4.

Table 4. Characteristics of the patients involved in studies I-III, at baseline. Mean (SD) and range are presented in continuous data for age (in years), BMI (in kg/m²) and 10-m MAX (in seconds). Distribution in MIRS grades is shown in percent.

	Study I	Study II	Study III
	N=10	N=51	N=43
Sex	6M/4F	20M/31F	18M/25F
Age	43 (10.7) 28-60	41 (9.7) 20-60	41 (9.1) 23-60
BMI	23.4 (4.0) 18.3-32.1	25 (5.4) ^a 17.1-37.5	24.4 (4.8) ^b 17.2-37.5
MIRS grade	1 0 (0%) 2 0 (0%) 3 0 (0%) 4 8 (80%) 5 2 (20%)	2 (4%) 1 (2%) 16 (31%) 28 (55%) 4 (8%)	0 (0%) 0 (0%) 16 (37%) 24 (56%) 3 (7%)
10-m MAX	7.5 (1.4) 5.3-9.3	8.3 (5.3) 4.6-37	7.5 (2.4) 4.6-16.9

Abbreviations: BMI, body mass index; MIRS, muscular impairment rating scale; 10-m MAX, 10 meters Timed walk in maximum pace.

^a BMI <18.5, n=4; BMI 30-35, n=6; BMI >35, n=4

^b BMI <18.5, n=3; BMI 30-35, n=6; BMI >35, n=1

4.1 Study I

Ten patients with DM1, six men and four women, mean (SD) age 43 (10.7) years, came at three occasions for repeated measurements, with one week in between each occasion. Most of the patients were classified as MIRS 4 (80%), and none was classified as MIRS 1-3 (paper I).

Timed 10-m walk

Timed 10-m walk showed high relative reliability with only small differences between comfortable and maximum pace, see Table 5, and the within-subject standard deviation was small in both, SEM 0.6 and 0.4. A post hoc paired t-test showed a systematic difference with a small effect size between occasion 1 and occasion 2 in the comfortable pace, Cohen's delta 0.28, and between occasion 2 and 3, Cohen's delta 0.21. There was no (confounding) main effect between occasions in the 10-m walk in maximum pace.

Static balance tests

It was possible for all still-standing open-eye tests (Feet Together, One Leg Stance, Tandem Stance) to be performed at all occasions by all patients. One Leg and Tandem Stance showed good to high relative test-retest reliability $ICC_{2,1}$ 0.87-0.98. "Feet Together" lacked relative reliability due to a ceiling effect, all patients but one could perform the test full-time – 60 seconds (ICC 0.31). There was great variability between occasions in the absolute variation values (SEM, repeatability and ME).

Dynamic balance tests

It was possible for all performance-based measures of functional balance skills (TUG, Step test and Walking in a Figure-of-Eight) to be performed at all occasions by all patients. The $ICC_{2,1}$ showed good to high relative reliability, Table 5. The variability, as measured by SEM, repeatability and ME, was much less as compared to the static test. Walking in a Figure-of-Eight showed a large standard deviation. In the Step test a systematic difference between occasion one and occasion two for the left-foot steps was shown, indicating a learning effect. Smallest real difference % (SRD%) is shown in Table 5.

Table 5. ICC, Repeatability and SRD% for gait and balance tests; OLS with eyes open, only right side.

	10-m COM	10-m MAX	TUG	STEP	OLS (EO)
ICC_{2,1}	0.91	0.94	0.83	0.88	0.95
Repeatability	1.8 sec	1.0 sec	1.9 sec	3.9 steps	8.4 sec
SRD%	18%	13%	19%	28%	78%

Abbreviations: OLS (EO), One leg stance (eyes open); SRD, smallest real difference.

4.2 Study II

Fifty-one patients with DM1, 20 men and 31 women, mean (SD) age 41 (9.7) years participated in the cross-sectional study. Thirty-two patients had not only distal muscle weakness, but also proximal weakness to a lower or higher degree, equivalent to MIRS grades 4 or 5. The remaining 19 patients had less weakness, equivalent to MIRS grade 1-3.

Reference values

Altogether 220 individuals (male/female 111/109) 20-59 years old, mean (SD) 37 (11.1) years, contributed to the reference data. Their body mass index (BMI) was mean (SD) 24 (3.6). The main results are presented in Table 6. The specific reference data for Timed walk, Timed Up & Go and Step test for each gender and age decade are presented in Paper I, Table 1.

Table 6. Reference values for the reference group as a whole, n=220. In seconds and steps.

	10-m COM	10-m MAX	TUG	STEP
Mean	6.6	4.7	7.5	21.2
CI95%	6.54-6.74	4.66-4.82	7.40-7.69	20.9-21.5

4.2.1 Comparisons

Comparison with reference group

A comparison between the patients with DM1 and the reference group was made using the specific age- and gender related mean values as matched data, Table 7. The Student's t-test was used to analyse differences in continuous data. The difference between the patients with DM1 and the reference group in the number of falls, was analysed with χ^2 -test. There was a statistically significant difference ($p < 0.001$) between the patients with DM1 and the reference group in all tests as well as in number of falls.

Table 7. Comparison between patients with DM1 and data from the reference group, analysis of difference with Student's t-test (P value). Mean (SD) for continuous data. Median and quartiles (1;3) for number of falls. The falls were dichotomised in '0-2' and '3 or more' falls.

	DM1	Reference group	P value
10-m COM	10.5 (1.4)	6.6 (0.2)	<0.001
10-m MAX	8.3 (1.5)	4.8 (0.2)	<0.001
TUG	10.4 (1.2)	7.6 (0.3)	<0.001
STEP	13 (1.6)	21 (1.2)	<0.001
Number of falls	1 (0;4.5)	0 (0;0)	<0.001

Comparison of isometric muscle force between patients with DM1 and reference values

A comparison between the patients with DM1 and age- and gender related reference values of isometric muscle force from published reference studies was made (Bäckman et al., 1995, Phillips et al., 2000). All muscle force means of the patients with DM1 were decreased in relation to the expected force, Table 8. The relative force (the force compared to reference values) was lowest for the whole group in the ankle dorsiflexors and the knee flexors, 52% and 53%, respectively.

Comparison between genders

A gender subgroup analysis was performed showing that the males were in absolute numbers stronger than females in hip flexors and knee extensors,

and no gender difference was shown in the knee flexor force, Table 8. However, in the ankle dorsiflexors the males were weaker than the females; the males had median 72 N, vs. 174 N for the females ($p=0.033$). In the analysis of force in relation to reference values, the males' relative force was lower compared to females. The relatively weakest muscle group in men was the ankle dorsiflexors (27%). Moreover, in relative figures the males were weaker than the females in the knee flexors (46% vs. 58%), which were the weakest muscle group in the females, Table 8.

In the dynamic balance tests there was a gender difference only in the number of steps, females had median 14 and males median 11 steps, $p=0.008$. No gender differences were shown in the Timed 10-m walk tests.

*Table 8. Results of force measurements (newton) in all patients with DMI, and by gender. The relative figures is the force compared to reference values. Mean (SD) or median (first quartile; third quartile) is presented. Analysis of difference in absolute muscle force between males and females was performed with Student's *t*-test for independent groups (*P* value); Mann-Whitney *U* test was used for the ankle dorsiflexors as the data was skewed.*

	All N=51	Males N=20	Females N=31	P value
Hip flexors ^a	85%	191 (44) 78%	155 (31) 89%	0.001
Knee extensors ^b	86%	317 (126) 77%	252 (61) 92%	0.016
Knee flexors ^b	53%	104 (44) 46%	97 (26) 58%	0.474
Ankle dorsiflexors ^a	52%	72 (44;125) 27%	174 (74;201) 76%	0.033

^a(Phillips et al., 2000) ^b(Bäckman et al., 1995)

Comparison between MIRS subgroups

The data from the patients with DM1 was divided into two groups for analysis of differences between the weaker patients (MIRS 4-5) and the less muscular impaired patients (MIRS 1-3). There was a statistically significant difference between the weaker and the stronger patients in all compared measures, the least significance ($p=0.014$) was shown in the number of falls, median 3 vs. 0 falls, Table 9. More men were classified to MIRS 4-5.

Table 9. Comparison between patients with muscular impairment: MIRS 1-3 and 4-5. Student's t-test and Chi2 are used for analyses of differences. Mean (SD) or median (first quartile; third quartile) is presented, as well as number (%).

	MIRS 1-3 (n=19)	MIRS 4-5 (n=32)	P value
Sex, χ^2	3M/16F	17M/15F	<0.001
Ankle dorsiflexors	200 (184;225)	61.6 (43;96)	<0.001
10-m COM	8.1 (2.1)	12 (5.7)	0.001
10-m MAX	6.1 (1.3)	9.7 (6.3)	<0.001
TUG	8.6 (2.1)	11.4 (5.0)	0.007
STEP	17.1 (3.9)	10.5 (8.5-1)	<0.001
ABC scale	91 (83;96)	62 (38;77)	<0.001
Number of falls, χ^2	0 (0;1.5)	3 (0;6)	0.014
Fear for falls, n (%), χ^2	3 (16%)	18 (56%)	0.004
Avoids activities due to fear for falls n (%), χ^2	3 (16%)	20 (59%)	0.001

4.2.2 Factors of importance

Factors of importance for functional balance impairment

Each muscle group showed a statistically significant correlation ($r_s = 0.39$ to -0.65 , p between 0.004 and <0.001) with the different dynamic balance tests

and timed 10-m walk, as factors of importance for functional balance impairment. The gait test and single leg muscle group with the greatest correlation was 10-m MAX and ankle dorsiflexors, $r_s = -0.65$ ($p < 0.001$). The 10-m COM and total muscle force showed $r_s = -0.71$ ($p = 0.001$). Knee flexor force was the most important single muscle group for TUG, $r_s = -0.61$, $p < 0.001$; and ankle dorsiflexor force for Step test, $r_s = 0.56$, $p < 0.001$.

Factors of importance for falls

Factors of importance for frequent falls showed to be the balance confidence assessed with ABC score, the ankle dorsiflexor muscle force and a larger time-difference between comfortable and maximum walking speed in 10-m walk (paper II).

A moderate negative correlation between number of falls and ankle dorsiflexor force (-0.38 , $p = 0.007$), and Step test (-0.36 , $p = 0.01$) was shown. Further, a moderate positive correlation was shown between falls and TUG (0.39 , $p = 0.005$). There was a strong negative correlation between number of falls and patient reported balance confidence in ABC, $r_s -0.52$, and $p < 0.001$. In the results of the uni-variate ordinal regression analysis an augmented risk of falling with 49% at a decrease of 10 units in the ABC scale was shown. The multi-variate analysis detected that a decrease of ten newton in ankle dorsiflexor force would infer 15% increased fall risk, and an increase in time-difference with one second between comfortable and maximum walking speed, measured over 10 meters, would increase the fall risk with 42%.

4.3 Study III

Forty-six patients with DM1 from the cross-sectional study were included at baseline in the longitudinal study. After three dropouts, data from 43 patients (18 men/25 women, mean (SD) 41 (9.1) years of age) were available for analysis at the five-year assessment (Y5). The results were analysed in total and by gender. Thirteen patients had worsened in MIRS-grade, and the change was statistically significant in both gender subgroups. At Y5 the mean (range) in BMI was 25.6 (17.5-39.4); $n=9$ had BMI 30-35; all other numbers were the same. The proportion of patients with BMI 30-35 had increased from 14% to 21%.

Isometric muscle force

A statistically significant force decrease was shown in all four examined leg muscle groups, mean change -8 to -15 N, p value between < 0.001 and 0.017 . For males, all muscle groups showed an absolute force decrease of statistical significance; for females this was only seen in the hip flexors ($p < 0.001$). In

absolute figures the change was significantly different between males and females in knee extensors and knee flexors. Analysis of change in relation to baseline force, however, showed a significant difference also in the ankle dorsiflexors; for the whole group the relative change in ankle dorsiflexors was mean -12%, although for males the relative change was -22% vs. -7% for the females, Table 10.

Table 10. Relative change in muscle force for all patients with DM1, and by gender. Mann-Whitney U test is used for analysis of difference between genders.

	All	Males	Females	P value
Hip flexors	-7%	-7%	-7%	0.82
Knee extensors	-6%	-11%	-1%	0.028
Knee flexors	-8%	-13%	-4%	0.013
Ankle dorsiflexors	-12%	-22%	-7%	0.034

Performance-based measures of functional balance

All dynamic balance tests and gait showed statistically significant deteriorations, with $p < 0.001$, Table 11. The timed 10-m walk (10-m MAX) showed a mean time increase of 1.8 seconds at Y5. The Timed Up & Go showed a mean increase of 2.4 seconds, and Step test showed a mean decrease of 2.6 steps compared to baseline, Table 11. No differences between genders were shown in the tests of 10-meter walk and functional balance.

Patient reported outcome measures

There was a minor but statistically significant reduction in ABC score, mean (SD) score change -7 (18), $p = 0.024$ for the whole group. The deterioration was larger for males, mean (SD) score change -10 (19), $p = 0.042$, the deterioration for females did not reach statistical significance.

The RW-index also showed deterioration, 56% got worse, $p = 0.003$, with no statistically significant difference between genders. The number of falls, as expressed in mean (SD), did not change. However, the proportion of patients experiencing at least one fall had increased from 58% to 77%. All males (100%) had fallen during the previous year, a statistically significant change, compared with 67% at baseline ($p = 0.031$). Twenty-one patients (49%) had

fallen three or more times within the previous year, as compared to only 14 (33%) at baseline. The number of patients who needed medical care was increased, 42% had reported need for care after falls at Y5 vs. 16% at baseline, $p=0.013$. Fear of falling was reported by 63% at Y5, compared to 37% at baseline, $p=0.007$.

Table 11. Timed 10-m walk and dynamic balance tests at baseline and year five (Y5). P value for change. N=43

Measures		Baseline	Y5	P value
10-m MAX (seconds)	Mean (SD)	7.5 (2.4)	9.3 (4.3)	<0.001
	Min-Max	4.6 – 16.9	5.1 – 24.2	
Timed Up&Go (seconds)	Mean (SD)	9.6 (2.4)	12.0 (5.4)	<0.001
	Min-Max	6.5 – 17.5	7.0 – 34.4	
Step test (steps)	Mean (SD)	13.3 (5.4)	10.7 (6.5)	<0.001
	Min-Max	0 – 23.5	0 – 22.5	

5 DISCUSSION

The most important finding in this thesis is the increasing number of harmful injuries, which the patients had experienced after falls. Further, we have linked loss of muscle force in lower extremities with decrease in dynamic balance. Lastly we also found a gender difference; there was a more prominent decrease in muscle strength in males after five years. We do not have data explaining the reason for this difference.

5.1 Methodological discussion

Measuring muscle force

The isometric muscle force measurements of the patients with DM1 were compared with reference data (Bäckman et al., 1995, Phillips et al., 2000). A limitation with the relative values when comparing with reference data is the reliability limits of the reference material. We did not collect this reference material ourselves; we had to rely on published data. A weakness in the method of measuring isometric muscle force by handheld dynamometer is the difficulty for an examiner to reliably measure strong muscles. This could result in reference values that are falsely too low in e.g. ankle dorsiflexors and knee extensors, at least in the case of the data for males. To decrease the risk of falsely reporting too weak a muscle force in strong muscles in our study, we utilised the wall as support, if needed. In the case a patient nevertheless was too strong, the break method could not be used, and the force was measured without the break. It is not believed that the break method could elicit a stretch-evoked response, but the force generated during muscle lengthening is shown to exceed maximum isometric force (Webber and Kriellaars, 1997).

An advantage of this longitudinal study is that the same examiner performed all measurements. The variability in readings obtained by handheld dynamometry can be kept to a minimum when only one examiner is used (Goonetilleke et al., 1994).

Measuring gait

The timed 10-m walk should not be regarded as a balance test, as it is a gait test. But the gait will be secondarily affected if the postural stability is impaired. This makes it useful as a performance-based measure of functional balance together with the Step test and TUG (Jarnlo, 2003).

We chose to measure *time* to walk 10 meters from a still-standing start, a straight forward walk of 10 meters in a long corridor, with a flying finish. This choice was made as we wanted to include the patients' sometimes slow start. The patients walked towards a target 2.5 meters beyond the 10-meter point. Hence acceleration was included but not deceleration. Our intention was to mimic a distance and a situation of a (large) zebra crossing. Reference values for gait *speed* (in m/sec or cm/sec) where no acceleration or deceleration is included are published, but were considered less suitable for us (Öberg et al., 1993, Bohannon, 2008, Bohannon and Williams Andrews, 2011).

Assessment of postural control

There are three main approaches to clinical balance assessments: a functional approach to identify fall risk; a systems approach to determine the underlying cause; and quantitative posturography (Horak, 1997).

The systems approach to determine an organ dysfunction or an underlying diagnosis, e.g. cerebellar dysfunction or sensory deficiency, was not within the scope of this thesis. The weakness in distal leg muscles, characteristic for patients with DM1, is thoroughly studied as one risk factor for falls among several others, and in combination the fall risk increases (Rubenstein, 2006). It has been shown that muscle strength reduction in nursing home residents with a history of falls was more severe, compared with those with no history of falls. The difference was most pronounced in the ankle dorsiflexors; (isokinetic) muscle torque was one tenth that of controls (Fukagawa et al., 1995).

Laboratory centre of gravity measurements with force platforms, giving a picture of how the centre of mass has moved over the base of support during different tests, have increasingly been used in postural control research. The use of force platforms in the clinic is not forecasted, and the laboratory setting was therefore rejected in investigations in the present thesis.

We chose not to use the well-renowned Berg Balance Scale (Berg, 1989) since the BBS was believed to have ceiling effects in the younger, well functioning, DM1 population. Instead we chose performance-based measures of functional balance skills: 10-meter walk in maximum speed; Timed Up & Go; and Step test, as the DM1 patients are believed to fall (often after tripping) in walking and stepping situations. The reliability study (paper I) examined these dynamic and also static balance tests in the patients with DM1. The static tests were less test-retest stable than the dynamic, and were consequently rejected. The dynamic balance tests in this thesis were chosen

as items resembling balance requiring daily activities. The anticipatory postural control could be seen as a component in both dynamic tests as well as in the gait tests.

Perceived balance confidence and walking ability

Our choice of balance confidence measurement instrument stood between two at that time available questionnaires developed to measure “fear of falling” (FES) (Tinetti et al., 1990, Hellström and Lindmark, 1999) or “perceived confidence in keeping balance, when doing different activities” (ABC) (Powell and Myers, 1995). Both questionnaires were utilised in the cross-sectional study (paper II) but only the ABC data have been reported.

Three main reasons contributed to the choice of ABC for the prospective study (paper III): 1) the questions of ABC were constructed in a positive way; 2) both ABC and FES included several activities at home, but the ABC included several activities in the community, versus only one in the FES. Further, we conducted a post hoc analysis after the cross-sectional study (paper II) which showed 3) large ceiling effects in the FES. Given the result of this analysis and that the studied patients with DM1 was between 20 to 60 years of age, the ABC seemed to be the most suitable questionnaire.

The RW-index has shown to be a statistically significant predictor for repeated falls: a sum score of eleven or less indicates a positive predictive value of 0.25 to fall two times or more during the next year. Nevertheless, the area under the resulting receiver-operating characteristic (ROC) curve was just 0.57, which is interpreted as a not so efficient classifier (Bergland et al., 2002). It may be used in the health care system as a simple tool to identify people at increased risk of falling, but has a ceiling effect in a healthier population.

Questionnaires with self-assessments in patients with DM1 are not easy to use for all patients, since reading may be impaired due to dyslexia, short-term memory may be impaired, as well as the ability to visualise a situation exemplified in a questionnaire (Gagnon et al., 2007b). Further, since writing may be difficult due to hand and finger weakness, questionnaires with multiple-choice question are preferred.

The evaluation methods for number of falls recommended with use of diaries, calendars or postcards were not chosen in the present thesis. An accelerometer worn day after day for years was not a viable choice, for integrity reasons as well as for expected compliance difficulties. Despite the

obvious risk for retrospective recall error, the method used by us was half-open questions at the assessment occasions.

5.2 General discussion

Reliability

The results of the first study show that Timed Up & Go and the Step test are reliable and test-retest stable performance-based measures of functional balance skills, feasible to use in a DM1 population, after a practice round. Therefore these tests were used to evaluate balance skills in the patients with DM1, and not the still-standing tests, which showed a large discrepancy in the measures of absolute variation. To evaluate postural control in locomotion, Timed 10-meter walk in maximum speed is preferred before the comfortable speed, showing no confounding effect between times and low absolute variation together with high relative test-retest stability.

Muscle force

The patients with DM1 as a group were significantly weaker than published reference data in all muscles of the lower extremities that we studied. The more severely affected patients, classified as MIRS 4-5, were likewise weaker than the less affected, as expected.

We found that there was a gender difference; females were relatively stronger than males in all muscle groups examined, compared to reference values, and in absolute numbers stronger than males in the ankle dorsiflexors. This was also reflected in the MIRS classification where 85% of the males had MIRS grade 4-5, vs. 48% of the females. The reason for this disparity is still to be investigated.

The most affected muscle group in males with DM1 was the ankle dorsiflexors, where the relative muscle force was 27%, compared to expected values, in contrast to 76% in females. For females the knee flexors were the weakest, 58% of the expected value, but in males the strength was still lower, at 46%. In this study the upper limb muscle weakness was only taken into account for the MIRS classification, which doesn't give enough data to generalise the gender differences further. We do not know if there is also a gender difference in the upper extremities.

After five years the deterioration in muscle force was significant for the whole group in all muscle groups. A gender subgroup analysis, though, revealed that the women had a statistically significant loss of muscle force

only in the hip flexors. In the long term, obviously, the progress in leg muscles was more prominent in the men. If this can be confirmed in additional studies it has to be taken into account in future therapeutic studies.

Timed 10-m walk, TUG, Step test

The first moments of walking and the Step test were very difficult for some individuals, as they had great difficulty to stand still before starting the tests. The use of the step strategy or the “changing base of support” strategy is normally used as a response to large perturbations but in these study patients this strategy showed up when trying to stand still. This might be evidence of a severely impaired postural control due to very weak distal muscles, the patients not being able to deal with any sway at all (Nashner, 1987).

The timed 10-m walk was impaired, already showing an increased time in the less impaired patients with DM1 in the cross-sectional study (II). Patients with MIRS 1-3 had 83% of the speed in the reference group in 10mCOM, 8.1 seconds vs. 6.6 seconds or 1.23 m/s vs. 1.5 m/s, respectively. The patients with MIRS 4-5 walked slower, mean 12 seconds (0.83 m/s). A pedestrian speed of 1.22 to 1.4 m/s is needed to cross a street with traffic light in proper time (Lundgren-Lindquist et al., 1983, Langlois et al., 1997).

The Step test requires stability in the supporting leg and anticipatory postural control in locomotion. It gives information on the functional balance skills, even if the patient fails to make one single step. The systematic difference between occasion one and occasion two for the left-foot steps in Step test indicated a learning effect. Thus, the mean of the right and the left steps was employed in the analysis to diminish the influence of such learning effect.

The well-renowned TUG test has in this study shown its feasibility also in the patients with DM1. It examines different aspects of postural control, but primarily the anticipatory aspect, including elements like rising, turning and sitting down. The TUG test time could give support for possible fall risk as well as functional mobility. Unfortunately, we did not use the expanded dual-task TUG, where the extra cognitive demand could further increase the discriminative value of the test (Hofheinz and Schusterschitz, 2010).

We found a statistically significant decrease in the performance of timed 10-m walk, TUG and the Step test after five years, both in the whole group and for males and females, respectively. This is interesting, as the females did not show as large force reductions. Could it be that the dynamic balance tests are more sensitive to changes? Could it be more important to follow these measures than the muscle force, at least in women?

Altogether, it seems important to use all three measurements to capture different aspects of the patients' impairment.

Falls, fear of falls and activity avoidance

Muscle weakness has been shown to be an important risk factor for falls (Wiles et al., 2006, Horlings et al., 2008). Avoidance of activities for fear of falling has earlier been shown to increase with a greater number of falls (Yardley and Smith, 2002). People living in the community over the age of 75 have, when asked, agreed to consequences of falling of 60% "I will be in pain" but also of 58% to "I will be embarrassed" and of 56% "I will feel foolish" (Yardley, 2003). It would be likely to presume that these fears are also common in patients with DM1.

The patients classified with $MIRS \geq 4$ reported a significantly larger number of falls, more fear of falling, and more avoidance of activities than the patients in the $MIRS \leq 3$ group.

The balance confidence was shown to be a measure reflecting the risks for frequent falls. The confidence is likely to diminish after experiencing repeated falls, it could be seen as self-evident, but it is satisfying to see that patients with DM1 are aware of their problems. A decrease in ankle dorsiflexor force diminishes the ground clearance capacity for the swing phase. This change in space between foot and ground increases the risk of stumbles and subsequent falls (paper II). The increased time-difference between comfortable and maximum walking speed shows a capacity of faster walking while the self-selected walking speed diminishes, which could be a sign of awareness of stumble risks.

The number of patients who reported a fall within the previous year had increased by Y5. All men had fallen. The effects of the falls were worse. This could also be due to a decreased muscle strength in the elbow extensors or the neck flexors, which have been reported in other studies (Harper, 2001, Mathieu et al., 2001). Weak elbow extensors namely will limit the possibility for the patient to protect their face, if falling forward; or to protect their head/neck if falling backwards with weak neck flexors.

Is it possible to prevent these falls? Could a "Nordic walking pole" or a cane help? The use of AFO's in patients with DM1 has not yet been sufficiently evaluated. These questions remain to be answered. In the meantime it is necessary to follow the patients with MIRS grade ≥ 3 regularly, at least yearly.

Concurrent with these falls, 63% of the patients reported fear of falling and 60% that they avoided activities due to fear of falling. Self-chosen activity restriction as a consequence of fear of falling, not necessarily preceded by an actual fall, is an independent predictor of decline in physical function in an elderly population (Deshpande et al., 2008). Feared consequences of falls are shown to be loss of functional independence and damage to identity (e.g. feelings of shame in embarrassing situations (Yardley and Smith, 2002).

Avoiding of activities may in turn lead to a sedentary life with several known negative side effects, as an increase of cardio-metabolic risk factors, diabetes type II, obesity and depression. The number of patients with BMI ≥ 30 had increased, which could be regarded as an indication of the accuracy of this assumption. This is information that has to be handled. The possibility to attend physiotherapists to exercise is limited; workouts with fun and easy programmes to music, like the “Friskis & Sveltis Open Doors”, are requested (Kierkegaard et al., 2011a). Aquatic exercise in a group is another possible way of practising physical training. First and foremost a positive way of coaching these patients to regularly attend physical activities is recommended. However, there are several obstacles that ideally should be dealt with: proximity, affordability, compliance and motivation.

Reference group

The results of the reference material collection show that during 20-59 years of age the walking speed in Timed 10m-walk and the performance time of TUG is quite constant and remains at a similar level for both genders in a Swedish population. During the sixth decade the number of steps in the Step test dropped (-3 steps) in males, but remained the same as in the fifth decade in females. The reason for this is unknown.

Postural control and age

The response to unforeseen balance threats changes with age (Lin and Woollacott, 2002). Younger people use their ankle muscles to a higher extent than older people. Both stable and unstable older people use a hip-dominated strategy in response to perturbations in stance. Unstable older people also use alternative strategies, such as bending the knees or using the arms to give support (Shumway-Cook and Woollacott, 2007). With faster perturbations the stepping strategy was used in older people, but not in younger (Lin and Woollacott, 2002). Changes in the motor systems affecting postural control are shown to follow the natural ageing process, and these changes can contribute to an inability to maintain balance. Age-related changes in the systems of postural control includes muscle weakness, impaired timing of the muscles involved in response to instability, and limitations of the adaptive

movements in response to different tasks and changing environmental demands (Shumway-Cook and Woollacott, 2007). Postural stability diminishes with older age and this could account for the increasing occurrence of falls in older adults (70s, 80s). This in turn could be an effect of a slowing in the anticipation process. Temporally delayed activation of anterior postural muscles in unstable older adults was shown in a study. Older adults had a significantly longer onset latency compared to younger adults and a decreased strength in lower extremity muscles (Lin and Woollacott, 2002).

If this occurs also in the DM1 patients with already weakened ankle muscles remains to be discovered, but a fact is that the step strategy is common in weaker patients with DM1 and in elderly people alike. In some ways the middle-aged patient with DM1 resembles an older person. Thus, it could be of interest to compare the findings in our cohort with research in older individuals.

Limitations

The muscle function aspect *power* has not been analysed in this thesis. It would be of great interest to investigate further the impact of muscle power on falls and postural control in DM1, as the “explosive strength” could yet be a more important factor than muscle force.

The differences between men and women in this study could be caused by a selection bias, as the longitudinal study was not a population based study. However, the drop-out analysis shows similar disease duration, gender and age in both groups.

There have been no evidence of other balance disturbances among the patients than those secondary to the muscle strength decline, but the present study has not analysed range of motion, deep sensibility, vision, cerebellar function or cognition. Aspects not covered by the tests used in this thesis are the reactive postural control, challenged in unforeseen perturbations; and the vestibular (Balatsouras et al., 2013), visual and somatosensory systems.

The study of timed walk has not included the measure of stride length. This could be a limitation as a recent study on patients with spinal muscular atrophy has shown that stride length, but not strength, fatigue or other gait variables, was associated with falls (Montes et al., 2013).

Another limitation of this thesis is that the psycho-social aspects of the dynamic balance impairment and falls not have been covered. These aspects are also very important and could be the object of further investigations.

5.3 Implications

The gait and dynamic balance tests showed a substantial mean deterioration accompanied by an increase of the proportion of patients avoiding activities due to fear of falling. We find it imperative to follow this patient group continuously, ask them about falls and refer them to physiotherapy treatment and follow-up using tests of dynamic balance (TUG and Step test), timed walk and muscle strength measurements. Walking aids, orthoses and electric wheelchairs are devices that may enhance continued activity participation, Table 12.

Table 12. Levels of disability and levels of intervention in DM1 in relation to ICF terminology.

	Intervention	Prevention
Health condition	No cure available for DM1	Genetic counseling Health promotion Nutrition
Impairments	Medication Pacemaker Rehabilitation therapy Balance exercise Physical fitness exercise	Prevention of development of further activity limitations
Activity limitations	Assistive devices Walking aids Ankle-foot orthoses Electric wheelchair	Preventive rehabilitation Prevention of development of participation restrictions
Participation restrictions	Accommodation adaptations Public education	Environmental change Employment strategies

It is notable that the progression of muscle weakness in the knee extensors, which are important for knee stability, was faster within the male group, and that all male patients had fallen in the previous year. Both males and females showed significant changes in the dynamic balance tests, but the deterioration in muscle strength was shown to be more severe in males. We thus recommend considering a more rigorous follow-up in patients with $MIRS \geq 3$.

The present study has broadened the possibilities of evaluating up-coming balance exercise therapy interventions, as well as other future studies in patients with DM1. As long as no cure exists the need for rehabilitation interventions and research will remain. This study will hopefully bring to the fore more research on postural control in patients with DM1, exercise studies aimed at preventing falls are strongly recommended.

CONCLUSIONS

We have studied muscle force and functional balance skills through gait and dynamic balance tests; as well as patient reported balance confidence, walking ability and falls within patients with DM1 during a five-year period.

The isometric muscle force and functional balance showed at the baseline assessment a moderate but statistically significant decrease compared to reference values (muscle force) and a reference group of healthy individuals (functional balance).

These variables also showed a substantial mean deterioration after five years, accompanied by an increase of the proportion of patients avoiding activities due to fear of falling. The activity avoiding behaviour could be seen as a consequence of this decreasing muscle force and functional balance impairment.

During the year prior to the five-year assessment all men had fallen. Males also showed a more prominent decrease in muscle force than females. We are inclined to believe that there is a gender difference in the progress of the impairment.

After five years the falls, although they did not increase in numbers, included a larger proportion of the patients. These patients encountered more severe injuries, which led to a higher degree of need for medical care services.

We find it imperative to follow this patient group continuously, ask them about falls and refer them to rehabilitation treatment and follow-up. Walking aids, orthoses and electric wheelchairs are devices that may enhance continued participation in different activities.

6 FUTURE PERSPECTIVES

Further studies are required to evaluate if rehabilitation interventions, including alternative balance strategies, in the long-term care of patients with DM1 could lead to a diminished rate of falls in the future. This could include a study on reactive and anticipatory postural control under computerised conditions.

Additionally, studies to further confirm the gender difference in loss of muscle strength are required.

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