LOWER LIMB MUSCLE IMPAIRMENT IN MYOTONIC DYSTROPHY TYPE 1: THE NEED FOR BETTER GUIDELINES

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ABSTRACT: In myotonic dystrophy type 1 (DM1), leg muscle weakness is a major impairment. There are challenges to obtaining a clear portrait of muscle strength impairment. A systematic literature review was conducted on lower limb strength impairment in late-onset and adult phenotypes to document variables which affect strength measurement. Thirty-two articles were reviewed using the COSMIN guidelines. Only a third of the studies described a reproducible protocol. Only 2 muscle groups have documented reliability for quantitative muscle testing and only 1 total score for manual muscle testing. Variables affecting muscle strength impairment are not described in most studies. This review illustrates the variability in muscle strength assessment in relation to DM1 characteristics and the questionable validity of the results with regard to undocumented methodological properties. There is therefore a clear need to adopt a consensus on the use of a standardized muscle strength assessment protocol.

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INTRODUCTION

Myotonic dystrophy type 1 (DM1) is the most common form of muscular dystrophy in adults[1]. It is a neuromuscular disease[2] resulting from a mutation on the 19q13.3 locus of chromosome 19, leading to an unstable repetition of cytosine-thymine-guanine (CTG) base pairs[3]. It is a multisystemic disease with various symptoms including loss of muscle strength, myotonia, dysphagia, and cognitive impairment, among others[4]. As recently stated in an international workshop report, the promising therapies in DM1 have led researchers and clinicians to believe that this population will soon have access to new therapeutic trials such as gene therapy[5]. As muscle strength is greatly affected in this population, it will be 1 of the main outcome measures to use to monitor disease progression. Indeed, lower limb (LL) weakness and a high level of fatigue are the 2 most important variables for disrupted social participation in DM1 patients[6]. However, presenting a clear and complete portrait of muscle strength impairment and properly assessing muscle strength in the context of therapeutic trials offers some challenges.

The first challenge is related to the description of muscle strength impairment according to the specific characteristics of the DM1 population. There are 4 DM1 phenotypes based on disease severity and age of onset (congenital, childhood, adult, and late-onset)[4]. The pattern of muscle strength impairment and the rate of progression of weakness is quite different in the congenital and childhood phenotypes compared with the 2 others[4]. This paper will focus on the adult and late-onset phenotypes. In the adult phenotype, symptoms generally appear in the second or third decade of life[4]. Affected patients develop, among other symptoms, myotonia and progressive loss of muscle strength[4]. The adult phenotype is heterogenous, as some patients have severe impairment affecting several systems early in life, while others are not as severely affected[7,8]. There is no clear cut-off between the 2 phenotypes, but the late-onset phenotype is characterized by older age of onset (>40years) and usually less severe muscle strength impairment[9]. In addition, the potential variability in rate of progression is an additional variable to take into consideration while describing muscle strength impairment. Indeed, the disease can progress to debilitating weakness in a few years, or it can be stable and benign for more than 20 years[1]. The prognosis is thus difficult to establish even though Mathieu et al.[1] have been able to estimate the average years of disease for each stage of the *Muscular Impairment Rating Scale (*MIRS). Description of muscle strength impairment in DM1

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

Abbreviations: DM1, Myotonic dystrophy type 1; CTG, cytosine-thymine-guanine; LL, Lower limbs; MIRS, Muscular Impairment Rating Scale; MMT, manual muscle testing; QMT, quantitative muscle testing; MRC, Medical Research Council; COSMIN, COnsensus-based Standards for the selection of health Measurements Instruments

Key words: Myotonic Dystrophy; Muscle Strength; Lower Extremity; Physiotherapy; Outcome Measure

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could thus be influenced by phenotypic variability (including CTG repeat length), age of onset, disease duration, and rate of progression.

The second challenge is associated with the different methods used in the international community to assess muscle strength [manual (MMT) or quantitative (QMT) muscle testing]. Several outcome measures are used to describe lower limb function in DM1, but specifically using quantified muscle strength measures allows one to clearly map weakness of all magnitudes in all muscle groups to obtain a better understanding of the related functional deficits and the natural history of the disease over time. On one hand, MMT does not require any equipment and is generally performed according to agreed-upon protocols[10]. Muscle strength, assessed by MMT, is most often rated on the 5-point Medical Research Council (MRC) scale, or its 10-point scale variant, the modified MRC scale[11]. On the other hand, QMT measures the level of maximum voluntary isometric or isokinetic force of a muscle group in a given position or through a given range of motion, using a force gauge (manual or fixed dynamometers)[12]. The 2 methods (MMT and QMT) are used in clinical practice and research. However, the methodological properties of QMT and MMT seem to have been explored only modestly in DM1. In addition, although the sensitivity of MMT to changes has been questioned for both clinical outcomes and evaluation of intervention effectiveness[13,14], MMT is still used in therapeutic trials.

The workshop on trial readiness in 2009[5] and the recent report[15] on Outcome Measures in Myotonic Dystrophy Type 1 (OMMYD-1) held in 2011 have raised concerns about the availability of methodologically sound outcome measures for muscle strength and the lack of natural history studies. However, no systematic review is available to provide a global picture of evidence-based data on muscle strength impairment in DM1. This is an essential step to clearly identify what is known and what still needs to be done in order to provide proper guidance to clinicians and researchers who are developing programs to document the natural history of the disease and methodological properties of muscle strength assessment procedures.

The objective of this paper is to perform a systematic literature review on lower extremity muscle strength impairment in individuals with the late-onset or adult DM1 phenotype while specifically documenting the variables affecting strength measurement in the DM1 population.

MATERIALS AND METHODS

A systematic literature review was conducted using the PubMed, Medline, and CINAHL databases with the following main keywords (English and French): myotonic dystrophy and strength (see appendices for the full term list). All articles published in French or English between 1980 and 2011 regarding muscle strength impairment in patients with the adult or late-onset DM1 phenotypes were included. The following exclusion criteria were used: 1) absence of muscle strength results, muscle strength results of upper limbs only or respiratory or smooth muscles only; 2) data collected in animals, and; 3) studies in patients with various neuromuscular diseases without specific results for a subsample of participants with DM1.

Three rehabilitation professionals (1 physiotherapist and 2 occupational therapists) performed the first screening of articles, based on title and abstract. Studies that met the inclusion criteria were kept for a further detailed assessment using a standardized extraction grid. The reference lists of retrieved articles were also consulted to cross-reference and find additional papers that also met the inclusion criteria. The extraction grid was developed according to COSMIN guidelines (COnsensus-based Standards for the selection of health Measurements Instruments)[16]. The COSMIN group developed a critical appraisal tool/checklist containing standards for evaluating the methodological quality of studies on the measurement properties of health measurement instruments (see http://www.cosmin.nl/). The extraction grid focused mainly on the protocol characteristics, methodological properties, and disease characteristics for muscle strength evaluation (phenotypes, disease duration, and selection of muscle groups). Additional information on muscle strength (frequency, severity) and muscle strength impairment rate of progression was also extracted.

RESULTS

The literature review led to a preliminary total of 103 articles. The review of the reference lists led to 6 additional papers (total n = 109). Seventy-seven articles were excluded according to the previously outlined criteria. A total of 32 articles were reviewed and thoroughly analyzed by 2 reviewers (EP, CG).

Documentation of disease characteristics for each study is presented in supplementary Tables S1 and S2 (available online)[13,17–46]. In terms of muscle weakness distribution, none of the studies described the results according to either adult or late-onset phenotype, and 7 studies also included other additional phenotypes. Overall, muscle strength assessment results are reported by pooled phenotypes. All lower extremity muscle groups (hip flexors, extensors, abductors, knee flexors and extensors, ankle plantarflexors, dorsiflexors, invertors, and evertors)

were evaluated in at least 1 study, with the exception of the hip adductors and the internal and external hip rotators (see supplementary Table S3, available online). The ankle invertors and evertors were also rarely assessed. Muscle strength assessment protocol characteristics are also presented in Tables S1 and S2. A majority of studies used only QMT, or both QMT and MMT, as the main outcome measure for strength. In a little over one-third of the studies, a reproducible protocol was reported (positioning and stabilization of the subject, number of measurements, instructions, encouragement and feedback given, order of tests, instruments used).

Concerning severity of muscle strength impairment, all studies that reported an overall assessment of muscle strength by MMT showed an average score of 4 or less on the MRC scale for all tested muscular groups[1,21,22,24,29,38,39,41]. According to these studies, the weakness profile in DM1 progresses from distal to proximal and does so in a symmetrical manner. One study suggested that significant proximal weakness was common in DM1[42]. For QMT, there is great variability among studies of muscle strength parameters (variations within the same muscle group, different units of measurement, and number of trials). In addition, no comparative values such as normative data or control groups were used except for 1 study[29].

Rate of progression was documented in most studies using a cross-sectional design with the exception of 6 longitudinal studies, including 2 over a one-year period[30,42], 1 over a two-year[32], 1 over a ten-year[29], and 2 over a period varying between 1 to 10 years[14,38]. From cross-sectional studies, Mathieu et al.[24] found a 0.95% decrease of MMT per year of disease duration (1.2% distal muscles, 0.7% proximal muscles/men = women), and a QMT decrease of 1.2 - 1.6% per year of disease duration for proximal muscles and of 2.0 - 3.0% per year for distal muscles (women < men). Hébert et al.[13] similarly reported an initial decline in the first 2 decades of the disease of 2.5% and 3.2% in QMT per year for the ankle evertors and dorsiflexors, respectively, followed by a rate of progression of about 1.5% (dorsiflexors) to 2.2% (evertors) for the subsequent years. A similar loss was reported by Whittaker et al.[14] (1.0 to 1.2%, and 0.2 to 0.4% in MMT per year for distal and proximal muscles, respectively). Using a longitudinal design, Sansone et al.[38] reported a 1.2% MMT decrease per year using a global score. The loss of muscle strength is described as linear, slow, and faster for distal muscles compared to proximal muscles[24]. Most people with DM1 progress to mild (44.7%) or moderate (50.9%) myopathy, and a lower proportion of people affected progress to a severe level of impairment (4.4%)[1].

With regards to methodological properties, only 2 muscle groups have documented intrarater and interrater reliability (good to excellent[13]) for QMT and only a total score for MMT (good to excellent[24,42]) (see supplementary Table S3, available online). The challenge associated with responsiveness to change of both methods has been discussed in 2 studies,[13,14] but no data are available. The smallest mean difference using QMT was calculated in 1 study and was reported to be roughly twice the standard error of measurement[13].

DISCUSSION

This systematic literature review of lower extremity muscle strength impairment in individuals with late-onset and adult DM1 phenotypes has allowed us to develop a global picture of the evidence-based knowledge of muscle strength. However, these findings raise a few relevant observations that question our current understanding of muscle strength impairment in DM1. We will first discuss observations related to muscle strength assessment more specifically, and then we will discuss potential implications of our findings with regard to characterization of muscle strength impairment.

Muscle Strength Assessment. Regarding the selection of muscle strength assessment methods, there is great variability in the choice of methods used. As seen in Tables S1 and S2, the QMT and MMT protocols vary considerably between studies, and they are often not sufficiently detailed to allow them to be reproduced. The protocols used also are fundamentally dissimilar (make/break test, peak/mean, contraction time, rest between repetitions, number of repetitions, positioning, and type of verbal stimulation), and that could influence the measurements obtained. Also, MMT protocols, when described, vary on many important key points such as positioning, uni- or bilateral assessment, and verbal stimulation that could significantly influence the result. In addition, the lack of agreement between studies with regard to the choice of the assessment protocols limits the comparisons considerably and prevents pooling of results to increase sample size.

Another issue that should be addressed is standardization of the strength assessment protocols. Complete information was only given in 1 paper (standardization of the protocol and training process)[13]. Developing and standardizing the administration protocol and the rater training process for each selected outcome measure are also major issues. Standardization of outcome measures and structured/systematic training for testing have previously been emphasized for clinical trials and natural history studies in neuromuscular disorders[12,13,47].

Considering the relatively low world-wide prevalence of DM1, a multicenter approach will be necessary to develop therapeutic trials. This may introduce additional challenges related to maintaining a good to excellent interrater reliability. However, with appropriate and standardized structured training, the sample size of clinical trials can be decreased significantly in some cases without any lessening of statistical power[48].

Although MMT and QMT have been described as acceptable methods for measuring muscle strength in individuals diagnosed with DM1[5], our results clearly show the lack of documented methodological properties.

Muscle Strength Impairment in Relation to Population Characteristics and Methodological Properties. All studies have pooled the findings for both late-onset and adult phenotypes, and sometimes for the congenital and infantile phenotypes as well. This pooling of results could lead to an over- or under-estimation of muscle strength impairments among the different phenotypes. Also, for natural history studies, it is essential to describe the phenotypes separately, as we do not know whether the rate of progression is the same. From an unpublished data analysis of a pool of 198 patients with DM1, we have found that the mean strength of ankle dorsiflexors, as assessed by QMT, was quite different between the adult (n = 158; 94.6 N) and the late-onset (n = 40; 167.5 N) phenotypes. Therefore, if we had pooled the data (109.4 N), muscle strength in the late-onset phenotype would have been clearly underestimated.

Although several studies describe muscle strength in DM1, the objective of only a few studies was to characterize the profile of muscle strength[1,13,14,21,22,24,27,29,30,34,39,41,42]. Other studies published results using muscle strength as biological markers for treatment efficacy (medication or exercise) or as part of a validation process of new techniques to assess muscle damage (e.g., magnetic resonance imaging) or functional status (e.g., Motor Function Measure). This may partly explain why some mildly affected muscles (e.g., knee flexors) have been assessed frequently while other key muscles have not been as frequently evaluated despite their known key functional role in other populations (e.g. hip stabilizers). In addition, only 1 study was designed to clearly document muscle strength as an outcome measure for clinical trials[13].

The progression pattern of muscle strength impairment from distal to proximal in late-onset and adult phenotypes is essentially supported by the results of studies that have used MMT[24,39,40]. In contradistinction, Nitz et al.[42] reported significant and common proximal weakness among DM1 patients. However, they did not report disease duration or age of onset. Reasons why proximal weakness has not been observed early on in the disease may be explained by the use of protocols that did not allow a valid measurement of proximal muscle strength and from the inability of MMT to detect mild to moderate weakness in proximal muscle groups that are among the strongest muscles, such as the hip. Assuming that the progression of disease is from distal to proximal, muscle strength impairment will inevitably reach the proximal muscles as disease duration increases. Thus, if the sample in the Nitz, et al. study consisted mostly of patients in an advanced stage of the disease, the authors could have consequently observed proximal weakness[43]. But leaving aside the duration of disease issue, the responsiveness and discriminative properties of MMT seem insufficient to identify proximal muscle strength impairment unless it is of a significant magnitude[13]. Therefore, this leaves the perception that the pattern of progression is systematically always from distal to proximal for all DM1 patients, which may not be the case; this still needs to be validated with protocols and instruments that have proper methodological properties. Concerning QMT, studies do not allow any conclusion regarding the relative severity of impairment for each muscle group over time on account of the great variability of parameters and the lack of comparison to normative data or a control group in most studies.

The protocols used to measure muscle strength in the vast majority of these studies are either insufficiently described or have significant methodological flaws, which in both cases does not allow one to draw firm conclusions on the profile of muscle strength impairment. The lack of documented methodological properties could influence results in many ways. For example, MMT has been reported to be less sensitive, especially in weak patients[13], and would not properly convey the slow progression pattern of the muscle strength impairment[14]. The results of Hebert et al.[13], Whittaker et al.[14], and Johnson et al.[29] raise questions about the use of MMT in monitoring the clinical course of patients and in assessing the effectiveness of interventions because of its low sensitivity to detect changes.

Finally, few studies have described the progression of muscle strength impairment over time[13,14,24,29,30,32,38,42]. The small number of longitudinal studies further limits the knowledge regarding the rate of progression of muscle strength impairment. Furthermore, none have categorized the myopathy according to each phenotype. The ability to generalize results to all DM1 patients is often also limited because of small sample sizes. A better

characterization over time of lower extremity muscle strength impairment in DM1 patients according to phenotype is essential in order to facilitate clinical decision making with regards to the monitoring of these patients. Additionally, further studies are needed to identify which specific lower extremity muscle strength impairments most contribute to the decline of functional autonomy in these patients in order to justify their use in clinical trials. Therefore, although several studies report data on muscle strength impairment in DM1, most could be partly misleading in their message, as several key variables were not taken into consideration in the design of the study.

The results show that, although previous studies have contributed significantly to our knowledge of muscle strength impairment in DM1, their findings must be interpreted with caution and within the limitations of the protocols used, including unknown or questionable methodological properties and strength protocols that have not considered all muscle groups. In DM1, the choice of the measurement method to assess muscle strength impairment should be based on specific criteria, including the one developed by the COSMIN initiative[16]: 1) known and acceptable psychometric qualities, including validity, reliability, and responsiveness; 2) feasible for a broad choice of muscles (proximal versus distal, upper versus lower limb versus spine); 3) clinical or research goals (assessing, treating, exercise program, gene therapy, etc.); and 4) type of study (cross sectional, longitudinal, randomized clinical trial, etc.). Other considerations related to the transfer of knowledge (feasibility of using the measures in a clinical setting; who will be the primary evaluator, a physician, physiotherapist, occupational therapist, or others) and the availability of equipment may also be taken into account.

Study Limitations. The risk for selection bias was minimized in this review by using 3 independent reviewers to screen articles. However, articles published in English and French only were reviewed. In addition, only published papers were reviewed and not theses or conference proceedings. Also, as we chose to focus on muscle strength impairments, other relevant studies using other outcome measures of lower limb function such as timed function tests or performance tests were not considered. Therefore, these findings are specific to muscle strength and are not inclusive of all the research that has been conducted on lower limb functional deficits in DM1.

CONCLUSION

This literature review illustrates the wide variability in the methods used to assess muscle strength. In addition, key variables that need to be taken into account while designing a study to document muscle strength impairment in DM1 have been outlined. The major issue to be addressed by future studies is documentation of methodological properties for muscle strength assessment, which is lacking at the moment. To overcome this situation, there is an urgent need to adopt an international consensus on the use of a standardized muscle strength assessment protocol with documented methodological properties to permit effective and efficient knowledge sharing among clinicians and researchers.

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