### Exercise Biology of Neuromuscular Disorders

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Exercise Biology of Neuromuscular Disorders

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Abstract

Neuromuscular disorders (NMDs) are chronic conditions that affect the neuromuscular system. Many NMDs currently have no cure, however as more effective therapies become available for NMD patients, these individuals will exhibit prolonged health- and/or lifespans. As a result, persons with NMDs will likely desire to engage in a more diverse variety of activities of daily living, including increased physical activity or exercise. Therefore, there is a need to increase our knowledge of the effects of acute exercise and chronic training on the neuromuscular system in NMD contexts. Here, we discuss the disease mechanisms and exercise biology of Duchenne muscular dystrophy (DMD), spinal muscular atrophy (SMA), and myotonic dystrophy type 1 (DM1), which are among the most prevalent NMDs in children and adults. Evidence from clinical and pre-clinical studies are reviewed, with emphasis on the functional outcomes of exercise, as well as on the putative cellular mechanisms that drive exercise-induced remodeling of the neuromuscular system. Continued investigation of the molecular mechanisms of exercise adaptation in DMD, SMA, and DM1 will assist in enhancing our understanding of the biology of these most prevalent NMDs. This information may also be useful for guiding the development of novel therapeutic targets for future pursuit.

Keywords

Duchenne muscular dystrophy, spinal muscular atrophy, myotonic dystrophy type 1, AMPK, PGC-1α
Introduction

Neuromuscular disorders (NMDs) are a heterogeneous group of inherited or acquired conditions that affect one or more components of the motor unit, which comprises the motoneuron, neuromuscular junction (NMJ), and skeletal muscle. Approximately 1 in 3,000 individuals are affected by these disorders, many of which are progressive, health- and life-limiting (Emery 1991). As such, the economic costs of the most prevalent NMDs, such as Duchenne muscular dystrophy (DMD), spinal muscular atrophy (SMA), and myotonic dystrophy (DM) type 1 are significant for patients and their caregivers ($30,000-$65,000/year), as well as for government health care systems (~$0.5-1billion/year) (Armstrong et al. 2016). The economic, social, and emotional burden associated with these conditions, combined with the actuality that most NMDs currently have no cure, emphasize the urgency to address unmet clinical needs and research knowledge gaps.

Among the most common signs associated with NMDs are skeletal muscle weakness and wasting. Myofiber atrophy may be primarily cell-autonomous, as observed for example in DMD, or it may occur secondary to degeneration of the innervating motoneuron, for instance in amyotrophic lateral sclerosis. Furthermore, the pathophysiology of SMA demonstrates that decrements in muscle quality and quantity occur via a combination of muscle and motoneuron dysfunction (Hamilton and Gillingwater 2013). The heterogeneity and complexity of this group of diseases is evidenced by conditions such as SMA and DM1, which present not only with neuromuscular impairments, but also with multi-system dysfunction, including cardiovascular and respiratory systems, as well as bone, cognitive, pancreatic, and gastrointestinal complications (Hamilton and Gillingwater 2013, Chau and Kalsotra 2015, Guiraud and Davies.
Current approaches to treat NMDs are predominantly symptomatic. New generation therapeutics, such as antisense oligonucleotide (ASO)- and adeno-associated virus-based gene therapy technologies (Rinaldi and Wood 2017), as well as small molecules, highlight the recent progress that has been made in treating NMDs. In fact, some of these, including Spinraza (nusinersen), Exondys 51 (eteplirsen), and Translarna (ataluren), have been recently approved by the US Federal Drug Administration or the European Medicine Agency (Rinaldi and Wood 2017). These strategies are not without their limitations however, including selective temporal therapeutic windows, narrowly defined target patient populations, as well as only modest efficacy in some instances (Havens and Hastings 2016). Knowledge gained from continued clinical trials of novel therapeutics in NMD patients, as well as the reverse translation of these findings into additional basic and pre-clinical studies, will likely assist in identifying more effective curative strategies.

As NMD patients adopt novel contemporary and future therapies, these individuals will undoubtedly exhibit prolonged health- and lifespans. It is very likely in this scenario therefore, that people with NMDs will embrace more active lifestyles. Thus, there is a critical need to expand our understanding of the effects of acute exercise and chronic training in NMD contexts. The exercise physiology of NMDs, in general, has been discussed previously, and interested readers are directed to excellent papers on this topic (Krivickas 2003, Anziska and Sternberg 2013). Moreover, the genetics and molecular biology of various NMDs, including current therapeutic technologies being examined therein, have been recently surveyed in detail elsewhere (Bowerman et al. 2017, Thornton et al. 2017, Guiraud and Davies 2017), and it is not within the scope of the current review to rigorously outline these further. Our goals here are first to provide
an overview of the disease mechanisms of DMD, SMA, and DM1, which are among the most prevalent NMDs. We follow this introduction to each NMD with a discussion of the exercise biology of the condition, including physiological, cellular, and molecular evidence gleaned from clinical and pre-clinical studies. In closing, we submit research questions on the exercise biology of DMD, SMA and DM1 that require further investigation.

**Duchenne muscular dystrophy**

DMD is an X-linked disorder affecting ~1/3,500 male births, making it the most common lethal hereditary disease (Birnkrant et al. 2018). DMD is characterized by proximal muscle weakness and wasting leading to loss of ambulation in the second decade of life and death by the third decade as a result of associated respiratory or cardiovascular complications. The molecular basis of DMD is a mutation in the *DMD* gene resulting in the absence of dystrophin protein (Birnkrant et al. 2018). In skeletal muscle, dystrophin is localized to the sarcolemma as part of the dystrophin-associated protein complex (DAPC), a heterogeneous transmembrane cluster with a variety of roles including stabilization between the cytoskeleton and extracellular matrix, as well as involvement in inter- and intracellular signalling (Guiraud and Davies 2017). The loss of dystrophin disrupts the DAPC rendering the sarcolemma susceptible to repeated mechanical-induced damage (Guiraud and Davies 2017). With each muscle contraction, large influxes of extracellular calcium (Ca\(^{2+}\)) enter the cell, which when combined with dysfunctional intracellular Ca\(^{2+}\) buffering, create a permissive environment for Ca\(^{2+}\)-sensitive proteases to ravage the myofiber. Repeated cycling of muscle degeneration followed by muscle stem cell-mediated regeneration eventually fails, which fosters the replacement of myocytes with noncontractile...
fibrotic tissue and fatty infiltrate (Ljubicic et al. 2014, Birnkrant et al. 2018). This pathological muscle remodelling accounts for the wasting and weakness observed in DMD patients. The only effective treatment available for DMD is glucocorticoids. These compounds slow the decline in muscle strength and function and delay the onset of respiratory, cardiac and orthopaedic complications (Birnkrant et al. 2018). Additionally, management of joint contractures and muscle extensibility through physiotherapy/rehabilitation is recommended during both the ambulatory and non-ambulatory phases (Birnkrant et al. 2018). Experimental studies support the use of gene-based therapies or small molecule treatments that aim to address the primary dystrophin deficiency or mitigate the resulting downstream sequelae (Guiraud and Davies 2017). For example, ASOs, like the recently FDA-approved Exondys 51, serve to restore the correct reading frame of the $DMD$ gene by inducing the skipping of exons adjacent to mutation sites. This, at best, produces a Becker muscular dystrophy-like phenotype, which is a less severe form of DMD caused by mutations that result in truncated but still somewhat functional dystrophin protein. A prevailing hypothesis asserts that therapies that are independent of the specific DMD-causing dystrophin mutation will be able to reach more DMD cases (Ljubicic et al. 2014, Guiraud and Davies 2017). Consistent with this, there is a strong body of evidence to suggest that increasing the expression in muscle of utrophin, an endogenous structural homologue of dystrophin, can mitigate the dystrophic phenotype (Dial et al. 2018, Ljubicic et al. 2014). Unlike dystrophin, utrophin is largely confined to the neuromuscular junction and myotendinous junction in skeletal muscle. Notably, utrophin is expressed at a significantly higher level in slow, oxidative myofibers, compared to their faster, more glycolytic counterparts. Furthermore, utrophin content is also enriched in extrasynaptic regions in slower,
more oxidative myofibers. This fiber type-specific utrophin expression pattern accounts, in part, for the greater degree of protection exhibited by slow, oxidative muscles against the dystrophic pathology (Ljubicic et al. 2014). Enhanced mitochondrial biogenesis and function, characteristics more typical of slow, oxidative muscle, as compared to fast, glycolytic tissue, also alleviate DMD (Ljubicic et al. 2014). Therefore, interventions that promote a phenotype shift towards a slower, more oxidative fiber type, which includes utrophin upregulation, may be an effective therapeutic approach in DMD.

**Exercise in DMD**

Although there still remain critical knowledge gaps with respect to the effects of chronic exercise on cardiac and respiratory muscle function in DMD patients (Spaulding and Selsby 2018), mild, habitual physical activity is a therapeutic modality that complements current neuromuscular (e.g., glucocorticoids) and rehabilitation (e.g., mobility devices) management strategies for DMD patients (Hyzewicz et al. 2015, Birnkrant et al. 2018, Kostek and Gordon 2018). For instance, the gold standard No Use is Disuse study by Jansen et al. (2013) demonstrated that assisted bicycle exercise training modestly, but significantly preserved muscle function in boys with DMD. As thoroughly discussed in recent, excellent contributions by Spaulding and Selsby (2018), Kostek and Gordon (2018), as well as Hyzewicz and colleagues (2015), exercise merits a more thorough evaluation as part of a holistic approach to improved patient care since in healthy individuals exercise produces beneficial adaptations to processes that are perturbed in DMD such as inflammation (Beavers et al. 2010), intracellular calcium homeostasis (Stammers et al. 2015) and oxidative stress (Powers et al. 2011). Thus, in light of these recent, comprehensive reviews on exercise in pre-clinical DMD models and DMD
participants (Hyzewicz et al. 2015, Kostek and Gordon 2018, Spaulding and Selsby 2018), which
readers are encouraged to peruse, here we focus on the potential molecular mechanisms of
exercise adaptation in dystrophic skeletal muscle. The identification of exercise-induced cellular
pathways that drive adaptive changes in DMD might provide valuable information for the
development of novel pharmacological therapies.

Mechanisms of exercise adaptation in dystrophic skeletal muscle

In the healthy condition, exercise activates 5' adenosine monophosphate (AMP)-
activated protein kinase (AMPK) via ATP depletion and the reciprocal elevations of AMP and
ADP. Chronic AMPK activation drives phenotypic remodelling in muscle through the regulation
of transcription factors and coregulators (Egan and Zierath 2013). For example, AMPK
phosphorylates and activates peroxisome proliferator-activated receptor (PPAR) γ coactivator-1α
(PGC-1α), a transcriptional coactivator and master regulator of neuromuscular plasticity. PGC-
1α coactivates numerous genes indicative of the slow, oxidative myogenic program, as well as
participates in a feed-forward loop via autoregulation. PGC-1α activity and expression are also
robustly stimulated by exercise (Egan and Zierath 2013). In addition to AMPK and PGC-1α,
molecules such as p38 mitogen-activated protein kinase (p38), calcineurin (CN), PPARδ, and
silent mating type information regulator 2 homolog 1 (SIRT1), are evoked by exercise (Egan and
Zierath 2013) and have been implicated in a variety of cellular functions that mitigate the
dystrophic pathology (Ljubicic et al., 2014). These processes include the regulation of
autophagy, improved myocellular Ca\textsuperscript{2+} handling, stimulation of mitochondrial biogenesis and
function, as well as other markers of the slow, oxidative phenotype, such as utrophin expression,
and induction of heat shock protein (HSP) content and activity (Ljubicic et al. 2014).
A single bout of exercise in mdx mice stimulates skeletal muscle AMPK and p38 phosphorylation status, and induces the mRNAs of PPARδ, PGC-1α, and SIRT1 (Ljubicic et al. 2014). Beyond this unfortunately, the mechanisms of exercise-induced muscle remodelling in DMD are unknown. It is reasonable to hypothesize however, that the molecular pathways that mediate acute exercise responses and training adaptations in the healthy condition, such as AMPK, PGC-1α, and PPARδ, might also do so in dystrophic muscle (Figure 1). Indeed, studies that genetically or pharmacologically activate these molecules support this concept. For instance, chronic treatment of mdx mice with the AMPK activator 5-aminoimidazole-4-carboxamide-1-β-d-ribofuranoside (AICAR) significantly increased utrophin expression along with increased markers of muscle oxidative capacity and induced a shift towards a slower muscle fiber type (Al-Rewashdy et al. 2015). Additionally, AMPK stimulation conferred a significant reduction in central nucleation, improved forelimb grip strength and decreased susceptibility to contractile-induced damage. Chronic AICAR administration also simulates corrective autophagy and ameliorates muscular dystrophy in mdx animals (Dial et al., 2018, Ljubicic et al., 2014).

Classic studies by the Jasmin and Spiegelman laboratories demonstrated that PGC-1α upregulates the expression of utrophin along with other genes associated with the neuromuscular junction (Angus et al. 2005, Handschin et al. 2007). Additionally, Handschin et al. showed that transgenic skeletal muscle-specific overexpression of the coactivator in mdx mice reduced numerous dystrophic indicators, such as centrally-located myonuclei and serum creatine kinase. These animals were also able to outperform mdx mice in a downhill running protocol, while exhibiting reduced signs of eccentric contraction-induced muscle damage. Similar alleviation of the dystrophic pathology was observed in mdx mice that overexpressed SIRT1 in muscle
(Chalkiadaki et al. 2014). Employing a more translatable methodology, Miura and colleagues demonstrated that chronic pharmacological PPARδ stimulation was effective at enhancing skeletal muscle utrophin content, coincident with evoking the slow, oxidative myogenic program in mdx mice (Miura et al. 2009). These molecular adaptations were associated with augmented muscle structure and function, as evidenced by an attenuation of the force drop caused by eccentric muscle contractions, as well as reduced contraction-induced sarcolemmal lesions. Pharmacological p38 activation with chronic heparin administration significantly augments utrophin protein expression in the mdx diaphragm (Amirouche et al. 2013). This is likely mediated, in part, by a post-transcriptional mechanism involving the enhanced stability of utrophin mRNA via the suppression of K homology splicing regulator protein (KSRP) activity.

As elegantly and comprehensively summarized by Michel (2007) and Lynch (2017), the Ca\(^{2+}\)-sensitive phosphatase CN and its downstream transcription factor target nuclear factor of activated T cells (NFAT) form the distal segment of a Ca\(^{2+}\)-regulated pathway that drives expression of the slow, oxidative myogenic program in dystrophic muscle. In short, CN permits NFAT to bind to the utrophin promoter and drive its expression in extrasynaptic regions of myofibers, which ultimately contributes to the augmented membrane stability, force-producing capacity, and improved histopathology in mdx mice engineered to exhibit elevated CN expression and activity. Dysregulated Ca\(^{2+}\) handling accounts for a significant share of the degenerative cascade in dystrophic muscle (Allen et al. 2016). HSPs have been shown to promote the restoration of Ca\(^{2+}\) homeostasis, as well as to mitigate other features associated with the dystrophic pathology such as inflammation (Thakur et al. 2018). Gehrig and colleagues (2012) demonstrated that inducing HSPs, by either pharmacological or genetic means, preserves
muscle function and slows progression of muscular dystrophy in mdx animals, as well as in the more severe dystrophin/utrophin double-knockout mice. Collectively, the evidence clearly indicates that the genetic or pharmacological activation of numerous molecules in dystrophic muscle, indeed those same proteins that are stimulated by exercise in the healthy condition, beneficially remodel the dystrophic phenotype in pre-clinical contexts. Future studies should aim to elucidate exercise-evoked mechanisms of adaptation, including whether recently discovered DMD disease modifiers, such as osteopontin, α-actinin-3, Jagged 1, or latent TGF-β-binding protein 4 are impacted by physical activity (Hightower and Alexander 2017).

**Spinal muscular atrophy**

SMA is the leading genetic cause of infant mortality and the second most prevalent autosomal recessive disorder after cystic fibrosis (Awano et al. 2014). This health- and/or life-limiting disorder occurs at ~1/10,000 live births. The most common and severe types I and II SMA account for approximately ~85% of all cases (Awano et al. 2014). These patients experience significant cardiorespiratory complications and most die ~24-36 months after birth (Awano et al. 2014). The less severe types III and IV SMA represent ~15% of the total and are diagnosed as early as 18 months old. Although patients with milder SMA generally live well into adulthood, a spectrum of motor impairments and secondary complications may manifest.

SMA is caused by homozygous mutations in the survival motor neuron (SMN) 1 gene, which encodes SMN protein (Hamilton and Gillingwater 2013). SMN protein has many important functions, including primarily spliceosome biogenesis (Bowerman et al. 2017). Mutations in SMN1 cause patients to rely solely on the virtually identical SMN2 gene to produce SMN protein. However, the majority (~80-90%) of SMN transcripts from SMN2 are truncated.
due to a C-to-T substitution at position 840 of exon 7. Despite being a translationally silent
difference, it nevertheless repeals the 5’ exonic splicing enhancer, which causes the spliceosome
machinery to exclude exon 7 from the mature SMN mRNA (Hamilton and Gillingwater 2013,
Bowerman et al. 2017). Consequently, these truncated SMN transcripts, known as SMN∆7, are
translated into similarly contracted and rapidly degraded SMN∆7 protein. However, ~10-20% of
SMN mRNA transcribed from SMN2 are full-length (FL) transcripts, which are synthesized into
functional FL-SMN protein. At present, the abundance of FL-SMN expressed from SMN2 genes
is the primary disease modifier in SMA.

The cardinal signs of SMA are the degeneration and death of α-motoneurons (αMNs),
NMJ dysfunction, as well as skeletal muscle wasting and weakness (Hamilton and Gillingwater
2013). While increasing FL-SMN abundance in the spinal cord (SC) certainly increases health,
fitness, and longevity in mice with SMA, optimal mitigation of the pathology necessitates
augmented FL-SMN levels in peripheral tissues including skeletal muscle (Bowerman et al.
2017). Thus, an intervention that elicits systemic effects, including the targeting of αMNs and
skeletal muscle in particular, should be considered when designing therapeutic strategies for
SMA (Talbot and Tizzano 2017).

The therapeutic efficacy of exercise in SMA patients

To our knowledge, the first study to report on the effects of chronic physical activity
specifically in SMA patients was by McCartney and colleagues (1988) in 1988. Here, a small
cohort (n = 3) of individuals with relatively mild SMA completed a nine week, three times/week,
progressive resistance exercise program, consisting of four sets of elbow flexion and bilateral leg
press not exceeding 70% maximal voluntary contraction. The authors observed that training lead
to improved dynamic strength in the arms and legs, greater isokinetic torque generation, and enhanced elbow flexor contractile properties. Furthermore, positive outcomes on feasibility metrics, such as signs of muscular damage, validated the tolerability and safety of exercise in this population despite the fact that historically, SMA patients have been advised against engaging in exercise training to avoid possible exacerbation of neuromuscular damage (Krivickas 2003, Anziska and Sternberg 2013).

Work by Lewelt and colleagues (2015) investigated the effects of a twelve week, progressive resistance training program, three times/week, in a larger group (n = 9) of children and adolescents with type II or type III SMA. In parallel with the previous literature, participant adherence was high (~90%) while training sessions were ~99% pain-free and no study-related adverse events occurred, reinforcing the notion that training is feasible and safe in SMA patients. Modest, but statistically significant training-induced increases in muscle strength were observed in the manual muscle testing of upper and lower body movements. Notably, motor function, evaluated with the Modified Hammersmith Functional Motor Scale-Extend, was also improved after training. The small sample sizes notwithstanding, these well-designed and -executed studies provide assurance that progressive resistance exercise training can be performed safely and without risk of harm, as well as demonstrate favorable adaptations in children, adolescents, and adults with SMA.

Endurance-type exercise training also elicits improvements in SMA patients. For example, Madsen et al. (2015) introduced a twelve week, home-based aerobic training program to a small cohort (n = 6) of type III SMA patients. Training was composed of 30-minute sessions on a cycle ergometer at 60-75% of predicted VO$_{2\text{max}}$ three times/week. Chronic exercise
significantly improved fitness (i.e., ~30% increase in VO$_{2\text{max}}$) without any increase in plasma creatine kinase levels, which would be indicative of training-induced muscle damage. Despite the increase in fitness observed in patients, there were no significant changes in functional outcomes, including the 6-minute walk test or the timed up-and-go. It is important to note here that all participants reported either no change or an increased feeling of fatigue in the activities of daily living (ADL) questionnaire. These results clearly indicate that careful consideration should be applied to the selection of training variables (i.e., frequency, intensity, time, type) in order to circumvent fatigue.

Endurance-type training adaptations in SMA patients are further described in a recent twelve week training study with non-ambulatory 4-7 year-olds with type II SMA (Bora et al. 2018). Here, participants ($n = 5$) performed 30 minutes of supervised arm cycling exercise at 60% of their maximum heart rate three times/week. The authors reported that the exercise regime was well tolerated, and that a significant improvement in endurance capacity was observed, as evidenced by augmented cycling distance and duration. Peripheral blood mononuclear cells were assayed for SMN expression, which revealed no alterations in SMN protein content over the course of the training program. Unfortunately, this analysis was not conducted in commonly biopsied peripheral tissues, such as skin or skeletal muscle, where SMN levels represent a more accurate biomarker of disease status. Finally, Montes and colleagues (2015) recently investigated the effects of combined aerobic and strengthening exercises in a Type III SMA patient cohort ($n = 12$) aged 10-48 years old. Participants performed aerobic, endurance-type exercise on a recumbent cycle ergometer five times/week, 30 minutes/day, whereas resistance-type exercise was performed three times/week with similar target duration. The investigation did not uncover
any deleterious effects of chronic exercise on strength, function, or fatigue. Further, all testing and intervention procedures were well tolerated without any serious adverse events. Percent-predicted VO₂max increased significantly (+5%) in the trained group compared to their control, sedentary counterparts, while modest, but not statistically significant improvements were observed in strength and functional measures in the trained SMA participants. The authors suspected that these small training-induced adaptations were partly due to impaired neuromuscular mitochondrial biogenesis and function. More work is required to address this interesting hypothesis.

Collectively, these studies demonstrate that both resistance- and endurance-type exercise programs are feasible, safe, and well tolerated in children, adolescents, and adults with SMA (Table 1). It is certainly worth noting that due to their small cohort sizes, the results of these important studies should be interpreted with some caution. Moreover, the clinical significance of enhanced fitness concomitant with limited improvements in strength and motor function observed in these studies remains unclear. However, the potential long-term benefit of increased fitness, strength, and function is clear. In addition, these investigations provide important guidance for clinical management of SMA patients and inform future study design of exercise in SMA.

The molecular mechanisms of exercise adaptations in SMA

Examination of the molecular mechanisms that drive exercise-induced neuromuscular remodeling in SMA is important because it increases our understanding of the basic biology of the disease, as well as facilitates the discovery of novel targets for future therapeutic investigation. Unfortunately, to date, no studies have pursued this cause in SMA patients. To
address this knowledge gap, Frédéric Charbonnier and colleagues published a series of elegant pre-clinical studies that explore the mechanisms of exercise adaptation in the neuromuscular system of SMA mice (Biondi et al., 2008; Chali et al., 2016; Grondard et al., 2005; Biondi et al., 2015). Grondard et al. (2005) was the first of these to detail exercise-induced molecular adaptations in mice with SMA. These animals, which recapitulated a relatively severe type II-like SMA phenotype, were subjected to a daily running program on a motor-driven running wheel beginning at postnatal day (P) 10. The trained animals exhibited improved clinical outcomes, including a ~60% prolonged survival rate, diminished muscle weakness, as well as enhanced motor behavior, as compared to sedentary SMA mice. Furthermore, the authors observed greater FL-SMN mRNA levels in the lumbar SC, as well as reduced loss of αMNs and skeletal muscle atrophy in the chronically active SMA mice. Remarkably, these training-evoked adaptations were revealed after as little as 3 days of running, which suggests that the upstream molecular machinery required to elicit these changes is intact and highly responsive in the SMA context. Biondi and colleagues (2008) later elaborate on a molecular mechanism driving these exercise-induced adaptations with a similar exercise protocol and SMA murine model. Here, daily exercise positively influenced NMJ morphology and transmission efficiency, while preserving αMNs in the soleus, plantaris, and tibialis anterior muscles of SMA mice. The authors also observed an increase in lumbar SC N-methyl-D-aspartate receptor (NMDAR) GluR epsilon 1 (NR2A) expression, a subunit of the NMDAR, in the trained SMA mice relative to the sedentary SMA group. To test whether the beneficial effects of exercise were dependent on the NMDAR, the specific noncompetitive NMDAR antagonist, MK-801, was then utilized. NMDAR blockade resulted in a significant reduction in the exercise-induced increase in
Together, these data highlight an important role for the NMDAR in exercise-induced neuromuscular plasticity in type II-like SMA mice.

A methodological challenge to using the type II SMA-like mice described in these studies is the rapid disease progression beginning at ~P9 and thus the relatively short lifespan of ~14 days. This short treatment window also limits the translational capacity of these exercise studies to the human SMA condition. To address these concerns, Chali and colleagues (2016) subjected mild SMA type III-like mice, which exhibit a typical lifespan, to a running- or swimming-based exercise training program for 10 months. They observed significant increases in muscle strength and endurance in response to both interventions. αMNs in the ventral horn of the SC were preserved in both trained SMA groups, as was NMJ structure and function. Interestingly, significant differences in the presence and/or magnitude of training-induced adaptations were observed between run and swim exercise. For example, the loss of larger, faster Chodl+ αMNs was limited by swimming only, whereas running selectively preserved ERRβ+ small, slower αMNs. It is important to note that all of the beneficial changes elicited by training, regardless of mode, emerged without changes in ventral lumbar SC SMN content. Whether there were alterations in skeletal muscle SMN levels was not reported. This study indicates that, at least in a relatively less severe model of SMA, the neuromuscular benefits of exercise training can occur in a SC SMN-independent fashion. This finding is not unprecedented, as improvement in NMJ biology and attenuated αMN attrition have been previously shown in SMA animals without accompanying elevations in SMN content (Talbot and Tizzano 2017).
Finally, Biondi et al. (2015) revealed some of the upstream, transcriptional mechanisms driving exercise-induced neuromuscular remodeling in SMA mice. Consistent with their previous work, the authors observed a rise in SMN protein in the SC with exercise training in type II-like SMA mice. The elevation in FL-SMN expression could be attributed to enhanced Ca\(^{2+}\)/calmodulin-dependent protein kinase II-protein kinase B (AKT)-cAMP response element-binding protein (CREB) axis signaling, which was likely mediated, in part, by a reduction in insulin-like growth factor-1 receptor (IGF-1R) content and downstream function. Furthermore, it was hypothesized that exercise-evoked downregulation of IGF-1R would attenuate extracellular signal-regulated kinase (ERK) and E26 transformation-specific domain-containing protein (ELK-1) activities, which serve to repress FL-SMN induction from \(SMN2\). This was supported by experiments in which SMA mice engineered with a knockdown of IGF-1R demonstrated increased CREB and reduced ELK-1 at the \(SMN2\) promoter, which was associated with augmented FL-SMN expression. The increased FL-SMN in the SMA/IGF-1R KO mice evoked similar exercise training-induced adaptations as those described by Grondard and colleagues above (2005), including improved motor function, preserved αMN content, and prolonged lifespan. Taken together, these studies by Charbonnier and colleagues provide a molecular basis for our understanding of how chronic exercise positively affects physiology and function in SMA (Figure 2).

AMPK and p38 MAPK might also act as alternative upstream mediators that contribute to exercise training adaptations in SMA (Dial et al., 2018). It is well established that endurance-type exercise training-induced benefits in healthy individuals occur due to, in part, the chronic activation of these enzymes (Egan and Zierath 2013). Chronic AICAR administration protects
NMJ morphology, as well as elicits increased myofiber size and greater proportions of type I fibres in relatively severe type I/II-like SMA mice, while treatment with the p38 activator celecoxib induces SMN mRNA stabilization by a human antigen R (HuR) protein dependent-manner in the brain and SC of these animals (Farooq et al. 2013, Cerveró et al. 2016). Based on these studies, it is therefore reasonable to hypothesize that AMPK- and p38-mediated signaling are among the mechanisms responsible for driving exercise adaptation in SMA (Figure 2). Additional work is necessary to confirm this, as well as to describe the SMN-dependent and -independent pathways by which training preserves or improves neuromuscular health and prolongs lifespan in SMA.

**Myotonic dystrophy type 1**

DM1 is the most common MD in adults and is the second most prevalent MD after DMD with an incidence of ~1/8,000 worldwide (Chau and Kalsotra 2015). It is an autosomal dominant trinucleotide repeat disease with multisystem involvement, prominently characterized by skeletal muscle weakness, wasting, myotonia and insulin resistance (Cho and Tapscott 2007). DM1 arises from a CTG microsatellite repeat expansion mutation in the 3’ untranslated region (UTR) of the dystrophia myotonica protein kinase (DMPK) gene (Chau and Kalsotra 2015). The phenomena of genetic instability and anticipation are common in DM1, which along with the occurrence of upstream CpG methylation, help explain the mechanisms underlying the various forms of DM1, including congenital, juvenile, and the more common adult-onset (Nakamori et al. 2013, Chau and Kalsotra 2015).

The disease mechanism of DM1 is due to DMPK RNA toxicity. Specifically, the expanded DMPK mRNA, which are resistant to nuclear export, aggregate in myonuclei and form
stable, double-stranded hairpin secondary structures. These CUG hairpins cause the
dysregulation of important RNA-binding proteins (RBPs), namely Muscleblind-like 1 (MBNL1)
(Chau and Kalsotra 2015). MBNL1 becomes sequestered to myonuclei due to its high affinity for
these hairpin foci that leads to MBNL1 loss-of-function. Dysregulation of MBNL1 therefore
drives alternative splicing, specifically an adult-to-fetal switch in pre-mRNA splicing patterns
(Chau and Kalsotra 2015). These immature isoforms are unable to meet the requirements of adult
skeletal muscle, the consequence of which manifests into DM1 clinical signs and symptoms. For
example, the myotonia of DM1 is largely attributed to the decreased expression of the muscle-
specific chloride channel (CLC-1) (Chau and Kalsotra 2015). The loss-of-function of MBNL1
causes alternative splicing of CLC-1 mRNA to include exon 7a, indicative of the developmental
isoform. CLC-1 exon 7a, which is normally excluded from the mature transcript, contains a
premature termination codon resulting in the nonsense-mediated decay of the mRNA and an
events in DM1 are largely attributed to the MBNL1 loss-of-function (Nakamori et al. 2013). Thus, the downstream functional consequences of the DM1 mutation are ultimately due to the
toxic gain-of-function of DMPK mRNA within myonuclei that causes MBNL1 loss-of-function.

There is no cure for DM1. Anti-diabetic and -myotonic drugs, physiotherapy, assistive
ambulatory devices, pacemaker or implantable cardioverter defibrillator, as well as cataract
removal surgery, are some of the modalities currently employed to manage disease-related
complications. Recent pre-clinical studies employing pharmacological technologies, for example
ASOs or clustered regularly interspaced short palindromic repeats/Cas9-mediated editing, as
well as small molecules, highlight exciting advances in potential DM1 therapies (Thornton et al.
However, there are considerable challenges associated with these interventions that currently preclude their governmental approval and availability to DM1 patients, such as their unreliable targeting to affected tissues in vivo, as well as the undefined optimal frequency of their administration (Havens and Hastings 2016). While these obstacles will very likely be surmounted eventually, it would be advantageous to identify lifestyle-based interventions that are safe, effective, and immediately deployable to improve muscle function and increase quality of life in DM1 patients.

**Exercise and DM1**

Pioneering work from Lindeman and colleagues (1995) sought to assess the effects of progressive strength training in patients with DM. The participants in this study were likely individuals with DM1, being described as the authors as having the “classical, adult type”. Participants trained at home three times per week using free-weights for 24 weeks targeting knee extension and flexion as well as hip extension and abduction. Knee torque measures did not differ between the trained group and the control, non-trained DM cohort. However, the majority of patients in the trained group reported improvements in ADL. Importantly, progressive strength training did not elicit signs of overwork damage as indicated by serum myoglobin levels, which did not differ from the non-trained, DM control group. Subsequently, Tollbäck and colleagues (1999) also utilized a resistance training paradigm that targeted the knee extensors, however their participants were DM patients and the protocol consisted of exercise three times per week for twelve weeks and was unilateral in nature with the opposite leg serving as the non-trained control. This experimental design took into account the limited number of participants (n = 6) who enrolled in the study. Here, resistance training evoked a significant improvement (+33%) in
strength without magnetic resonance imaging or histological evidence of muscle damage. Thus, the available evidence, albeit quite limited, suggests that resistance-type training in individuals with DM1 is safe and effective at increasing strength and improving ADL.

To our knowledge, Wright et al. (1996) were the first to investigate endurance-type training in individuals with DM. Here again unfortunately, this early work did not specify whether the participants were DM1 or myotonic dystrophy type 2 (DM2) patients. The study consisted of five DM participants whose training consisted of walking at 50-60% of maximum HR for 15 minutes for three weeks, followed by an increased duration of 20-30 minutes for the remaining nine weeks (Wright et al. 1996). Four of the five DM patients showed an improvement in peak VO\textsubscript{2} (mean of the five participants = + 9.0 ± 3.7%) on a graded exercise test after twelve weeks of physical activity, while three of five demonstrated an increase in peak power output (mean of the five participants = + 6.4 ± 6.1%). Training adherence was 83% and low subjective scores for perceived exertion, soreness and tiredness were recorded, which suggests that the training protocol was feasible, well tolerated and safe. The first examination of aerobic exercise training in DM1 patients was conducted almost a decade later by Ørngreen and colleagues (2005). The study recruited 17 patients, however five were excluded due to low compliance. The remaining twelve participants trained on a cycle ergometer at a heart rate corresponding to a work intensity of 65% VO\textsubscript{2max} for 30 minutes per session, five times/week for twelve weeks. There was a 92% adherence to the training schedule in nine of twelve patients. Aerobic training significantly improved VO\textsubscript{2max} by 14% and maximal workload by 11% in DM1 patients. Plasma creatine kinase levels did not change with increased physical activity, indicating that the training protocol did not induce muscle damage. Capillary density tended to increase
with training, whereas muscle fiber cross-sectional area, for both type I and IIa fibers, significantly increased. In this context, it would have been interesting to determine whether muscle strength also improved in response to cycle training. This, along with augmented aerobic fitness, might help explain, in part, the self-reported changes in ADL, which generally improved with training (Ørngreen et al. 2005). In summary, endurance-type training is well tolerated, safe, and augments cardiovascular fitness and self-assessed ADL in DM1 patients. The impact of aerobic training on alleviating DM1 symptoms such as myotonia, insulin resistance, and muscle weakness remain to be examined. It is also worth noting here that Ørngreen and colleagues (Ørngreen et al. 2005) preselected participants for their potential to complete the training regime. Although many continued to train after the twelve week program, the fact that five of seventeen participants withdrew from the study suggests that compliance may be a potential barrier to this type of exercise prescription in DM1.

Manual dexterity is associated with ADL independence and social participation in DM1 (Kierkegaard et al. 2011). To this end, Aldehag and colleagues (2005) examined the effects of hand training on strength and function in a small group of individuals with DM1. Their first study consisted of five DM1 participants who competed twelve weeks of dynamic hand strength-endurance exercises performed three times/week. Examples of the mass wrist and finger movements included flexion and extension of all fingers together except the thumb, while isolated finger and thumb exercises targeted each digit individually. On average, the participants completed 95% of all training sessions. Muscle force and fine motor control significantly improved post-training, and a positive change in self-rated occupational performance was also noted. In their subsequent investigation, the authors conducted a randomized controlled trial
(RCT) employing a cross-over design with the aim of confirming and extending their previous findings. Twelve weeks of dynamic hand training, three times/week, was again utilized, albeit in a larger cohort of 35 DM1 patients. Ten individuals dropped out of the study, while only thirteen participants exhibited acceptable (i.e., ≥ 75%) adherence. The hand training program had significant, positive effects on wrist flexor force, as well as self-perception of occupational performance and satisfaction of performance. Using the minimal clinically important values for the Canadian Occupational Performance Measure and Assessment of Motor and Process Skills, the authors observed that on an individual level, improvements were in general apparent after the training period (Aldehag et al., 2013). Collectively, these studies by Aldehag et al. (2005; 2013) demonstrate that this highly accessible, low-cost and -impact modality increases performance and satisfaction in ADL with no detrimental effects. As the authors noted, future studies should aim to advance our understanding of the personal and environmental factors in DM1 that may contribute to enhance intervention adherence rates.

In an effort to address some of the limitations of the few, existing studies of exercise training in individuals with DM1, such as short duration and small sample sizes, Brady and colleagues (2014) retrospectively analyzed clinical information of 63 DM1 patients to determine whether there was an association between long-term habitual physical activity and muscle strength. It is important to note that, to date, this is the only study that has controlled for both age and CTG repeat length between experimental groups. The data indicate that DM1 patients with midrange CTG repeat size (i.e., 100-500 CTG repeats) who self-reported habitual exercise participation (i.e., including all modes of physical activity, more than twice/week, for at least 1 full year; n = 31) outperformed their sedentary, control counterparts (n = 32) in grip strength, as
well as elbow flexion and knee extension torques. Given that in a recent survey of 200 DM1 patients, 69% stated that they aspire to do more exercise (Gagnon et al. 2013), and that resistance- and endurance-type exercise training modalities are feasible, safe, and generally well-received in individuals with DM1 (Kierkegaard et al. 2011), this area of research is primed to advance with large RCTs designed to identify the optimal training regimes for DM1 patients (Table 2). These data will in turn provide strong, evidence-based recommendations for exercise as a management strategy for DM1.

**Mechanisms of exercise biology in DM1**

The underlying mechanisms by which chronic exercise, regardless of modality, improves strength and function in DM1 are unknown. However, recent pre-clinical studies using pharmacological approaches to activate AMPK, an endogenous molecule that drives exercise adaptations in skeletal muscle, provide some insight. Treatment of cultured myoblasts derived from DM1 patients with the anti-diabetic compound metformin (MET) normalized the missplicing of six transcripts implicated in muscle biology, including the insulin receptor, troponin T2, as well as the sarcoplasmic/endoplasmic reticulum Ca$^{2+}$ ATPase (Laustriat et al. 2015). Moreover, over 400 alternative splicing events were modulated in DM1 human embryonic stem cell-derived mesodermal precursor cells treated with MET. In vivo studies support and extend this cell culture-based investigation of AMPK in DM1. Indeed, 7 days of daily AICAR administration to chronically activate the kinase in the human skeletal actin-long repeat mouse model of DM1 was effective at either fully or partially correcting several abnormal characteristics of skeletal muscle at the physiological, cellular, and molecular levels (Brockhoff et al. 2017). For example, myotonia was reduced, which was caused, in part, by increased
skeletal muscle CLC-1 protein content due, in turn, to a normalization of CLC-1 mRNA splicing that occurred coincident with a reduction in myonuclear foci. It is reasonable to suspect therefore that via an AMPK-mediated pathway, exercise training ameliorates DM1-associated myopathy, in part, through correction of MBNL1 biology (Figure 3). Testing this hypothesis should be part of a larger effort to identify the molecular mechanisms of exercise adaptation in DM1 (Dial et al., 2018).

Summary and Future Perspectives

Many NMDs are progressive, health- and life-limiting, and have no cure. As such, these disorders, including some of the most prevalent such as DMD, SMA, and DM1, bear significant economic and social burdens. Recent advances in gene-based therapeutics, ASOs for example, which address proximal disease mechanisms, are promising therapeutic avenues for NMDs (Talbot and Tizzano 2017). Indeed, nusinersen, eteplirsen, and ataluren are all recently approved gene therapy-based drugs that inspire hope for the NMD community notwithstanding the biological and practical limitations inherent to each approach. Despite historical, anecdotally negative connotations of exercise training in NMDs (Krivickas 2003), the scientific evidence summarized in this review confirms that endurance and resistance-type exercise interventions in DMD, SMA, and DM1 are safe and feasible. This declaration presumes that training principles are intelligently designed so as not to exacerbate the pathology, and acknowledges that the therapeutic window for exercise may be limited depending, in part, on the nature and progression of the NMD.

Moving forward, the pressing questions that remain include identifying the optimal exercise prescription (i.e., mode, frequency, intensity, duration) for each NMD, as well as to
acquire the knowledge necessary to personalize the prescription for each NMD patient. Furthermore, the molecular mechanisms of exercise responses and training adaptations in DMD, SMA, and DM1 have yet to be resolved. Pre-clinical studies suggest that for example, AMPK, p38, and CN-NFAT pathways, which drive exercise-induced plasticity in the healthy condition (Egan and Zierath 2013), are also very likely involved in exercise-evoked remodeling in NMDs. Further pre-clinical and clinical investigation of the molecular mechanisms of exercise in DMD, SMA, and DM1 is important because it will expand our understanding of the biology of these most prevalent NMDs, as well as assist in identifying novel therapeutic targets for future pursuit. In all, concerted efforts by those in the NMD community will continue to be required in order to advance the implementation of exercise prescription as an effective therapeutic modality, as well as exercise as a strategy for basic therapeutic discovery, for individuals with compromised neuromuscular systems.

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Conflict of Interest Statement

The authors have no conflicts of interest to report.
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368.

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Figure Legends

**Figure 1. Potential cellular pathways in skeletal muscle for exercise adaptation in Duchenne muscular dystrophy.** Pre-clinical studies in dystrophic mdx mice provide some indication of the mechanisms that drive exercise-induced skeletal muscle plasticity in DMD. Acute exercise upregulates AMPK and p38 activation status, coincident with the elevation of SIRT1, PPARδ, and PGC-1α transcripts in mdx mouse muscle (Ljubicic 2012). Complementary investigations capitalize on the availability of pharmacological compounds, such as AICAR or heparin, which stimulate discrete molecules that are also activated by physical activity, or utilize genetic strategies to induce the expression and/or activity of exercise-responsive proteins, for example transgenic overexpression of PGC-1α or HSPs. Downstream events, including the stimulation of corrective autophagic signalling, promotion of the slow, oxidative myogenic program, and the transcriptional and post-transcriptional increase in utrophin expression, contribute to structural and functional improvements in dystrophic skeletal muscle. Solid lines indicate established connections between events. Dashed lines refer to potential linkages between steps. Question mark indicates alternative, undiscovered pathways and/or mechanisms. Arrows illustrate activation, while horizontal line indicates p38-mediated inhibition of KSRP function.

**Figure 2. Putative mechanisms of exercise-induced neuromuscular plasticity in spinal muscular atrophy.** Studies of physical activity or small molecules in SMA mice demonstrate possible pathways of exercise adaptation. Activation of upstream molecules, for example AMPK, CaMKII, and p38, may initiate a signalling cascade that results in an
increase in FL-SMN expression in the neuromuscular system. Exercise-evoked alterations in skeletal muscle and αMNs might occur in both SMN-dependent and SMN-independent fashion. These beneficial adaptations result in enhanced healthspan and lifespan of mice with SMA. Dashed lines refer to potential linkages between steps. Question marks indicate alternative, undiscovered pathways and/or mechanisms. Arrows illustrate activation.

Figure 3. Mechanisms that may drive skeletal muscle exercise adaptations in myotonic dystrophy type 1. Potential mechanisms of exercise-induced muscle plasticity in DM1 are largely unknown. Pharmacological activation of AMPK, which is also well known to be robustly and reproducibly stimulated by exercise, causes the normalization of alternative splicing in pre-clinical models of DM1 in vivo and in vitro. This is likely due to the release of MBNL1 from myonuclear foci, as well as due to other undefined mechanisms. The correction of mRNA processing is associated with the upregulated expression and function of encoded proteins, and improvements in skeletal muscle structure and clinical function. Dashed lines refer to potential linkages between steps. Question marks indicate alternative, undiscovered pathways and/or mechanisms. Arrows illustrate activation.
Table 1: Summary of exercise studies in participants with SMA

<table>
<thead>
<tr>
<th>Exercise mode</th>
<th>Participant cohort size</th>
<th>SMA type</th>
<th>Exercise protocol</th>
<th>Safety</th>
<th>Adherence</th>
<th>Effects</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm cycle ergometer</td>
<td>7</td>
<td>Type II</td>
<td>12 week training program; 3x per week; 30 minute sessions at 60% MHR</td>
<td>Exercise training was well tolerated; no reports of myalgia</td>
<td>Two participants dropped out</td>
<td>Increase in cycling distance and duration at weeks 6 and 12 compared to pre-exercise values; no change in peripheral blood SMN expression</td>
<td>Bora et al., 2018</td>
</tr>
<tr>
<td>Leg cycle ergometer</td>
<td>8</td>
<td>Type III</td>
<td>12 week training program; 2-4x per week; 30 minute sessions at 60-75% VO_{2max}</td>
<td>No training-induced increases in plasma creatine kinase</td>
<td>Two participants dropped out</td>
<td>27% increase in VO_{2max}; 3 patients reported improved muscle strength, 2 reported increased levels of activity, 6 reported increased fatigue</td>
<td>Madsen et al., 2015</td>
</tr>
<tr>
<td>Leg cycle ergometer; resistance exercise</td>
<td>14</td>
<td>Type III</td>
<td>6 month training program; 5x per week; whole body resistance training, 3x per week; 30 minute sessions; 60-80% 1RM</td>
<td>Exercise was well tolerated; no adverse events reported</td>
<td>12 participants completed the exercise training protocol</td>
<td>~5% increase in VO_{2max}; no change in MMT; no change in 6MWT or clinical measures of motor function</td>
<td>Montes et al., 2015</td>
</tr>
<tr>
<td>Resistance exercise</td>
<td>9</td>
<td>Type II &amp; type III</td>
<td>12 week training program; 3x per week; progressive resistance training</td>
<td>Training sessions were 99.5% pain-free; no adverse events reported</td>
<td>High participant adherence (90.4%)</td>
<td>Increased muscle strength revealed by MMT; improvement in MHFMSE score</td>
<td>Lewelt et al., 2015</td>
</tr>
<tr>
<td>Resistance exercise</td>
<td>3</td>
<td>Not stated - likely to be mild SMA</td>
<td>9 week training program; 3x per week; progressive resistance training from 40-70% MVC; single arm and bilateral leg</td>
<td>Muscle biopsy and computerized tomography revealed no training-induced muscle damage</td>
<td>All participants completed training</td>
<td>Improved dynamic strength in the arms and legs; greater isokinetic torque generation, and enhanced elbow flexor contractile properties</td>
<td>McCartney et al., 1988</td>
</tr>
<tr>
<td>Resistance exercise</td>
<td>3</td>
<td>Not stated - likely to be type III/IV</td>
<td>12 month training program; 4x per week; whole body resistance training</td>
<td>Not stated</td>
<td>Participants did not experience overwork weakness.</td>
<td>Elbow flexion was not reported due to the lack of initial strength; maximal knee extension force increased ~100%</td>
<td>Milner-Brown and Miller 1988</td>
</tr>
</tbody>
</table>

6MWT = 6 minute walk test; MHFMSE = Modified Hammersmith Functional Motor Scale-Extend; MHR = maximal heart rate; MMT = Manual Muscle Testing; MVC = maximal voluntary contraction; RM = repetition max; SMA = spinal muscular atrophy; SMN = survival motor neuron.
<table>
<thead>
<tr>
<th>Exercise mode</th>
<th>Participant cohort size</th>
<th>DM type</th>
<th>Exercise Protocol</th>
<th>Safety</th>
<th>Adherence</th>
<th>Effects</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Habitual physical activity</td>
<td>63</td>
<td>DM1</td>
<td>Retrospective study; participants were habitually active &gt; 2x per week</td>
<td>Not stated</td>
<td>Not stated</td>
<td>Mean handgrip strength, knee extension torques and elbow flexion torques higher in active cohort versus sedentary</td>
<td>Brady, MacNeil, Tarnopolsky, 2014</td>
</tr>
<tr>
<td>Hand resistance training</td>
<td>35</td>
<td>DM1</td>
<td>12 week training program; 3x per week</td>
<td>Not stated</td>
<td>Ten participants dropped out; 13 participants had acceptable adherence (&gt; 75%)</td>
<td>Isometric wrist flexor force improved post-training; no change in handgrip force; satisfaction and change in self-perception of occupational performance increased</td>
<td>Aldehag et al., 2013</td>
</tr>
<tr>
<td>Resistance and endurance exercise</td>
<td>35 (n = 17 trained; n = 18 sedentary)</td>
<td>DM1</td>
<td>14 week training program; 2x per week; 60 minute group-training programme at 60% MHR</td>
<td>One participant demonstrated abnormal ECG, otherwise no adverse events reported</td>
<td>11/18 participants ≥ 75% attendance</td>
<td>Mean 6MWT increased (P &gt; 0.05) in the trained group by 9m</td>
<td>Kierkegaard et al., 2011</td>
</tr>
<tr>
<td>Leg cycle-ergometer</td>
<td>12</td>
<td>DM1</td>
<td>12 week training program; 5x per week; intensity of 65% of VO$_{2\text{max}}$; 35 minute sessions</td>
<td>Plasma creatine kinase was unchanged</td>
<td>76% adherence to training program</td>
<td>Training improved VO$_{2\text{max}}$ by 14%, maximal workload by 11%; increased type I and IIa fibre cross sectional area; no change in capillary density</td>
<td>Ørngreen et al., 2005</td>
</tr>
<tr>
<td>Hand resistance training</td>
<td>5</td>
<td>DM1</td>
<td>12 week training program; 3x per week</td>
<td>Not stated</td>
<td>Not stated</td>
<td>Increase in muscle force of wrist and finger extensors and flexors of the dominant hand; no difference in grip force; improved fine motor control in both hands; participants rated high occupational performance and satisfaction</td>
<td>Aldehag et al., 2005</td>
</tr>
<tr>
<td>Resistance training</td>
<td>9</td>
<td>DM</td>
<td>12 week training program; 3x per week; progressive resistance training with 3 x 10 repetitions 80% 1RM</td>
<td>No histological evidence of increased muscle damage with training</td>
<td>6/9 participants completed training program</td>
<td>1 RM increased post-training; no change in peak isokinetic torque; no difference in muscle cross sectional area; no effect on fiber type distribution</td>
<td>Tollbäck et al., 1999</td>
</tr>
<tr>
<td>Training Type</td>
<td>Study Participants</td>
<td>DM Type</td>
<td>Training Details</td>
<td>Rating of Perceived Exertion</td>
<td>Adherence</td>
<td>Outcome</td>
<td>Reference</td>
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<tr>
<td>Aerobic training</td>
<td>5</td>
<td>DM</td>
<td>12 week training program; 3x per week; 15-30 minute session walking at 50-60% of MHR</td>
<td>Low</td>
<td>83%</td>
<td>Decrease in submaximal heart rate and systolic blood pressure; four of the five DM patients showed an improvement in peak VO₂</td>
<td>Wright et al., 1996</td>
</tr>
<tr>
<td>Resistance training</td>
<td>33 (n = 19 trained; n = 14 sedentary)</td>
<td>DM</td>
<td>24 week training program; 3x per week; progressive resistance training; 60–80% 1RM</td>
<td>No change</td>
<td>18/19</td>
<td>No training effect observed in strength measures and endurance tests; improvement in functional metrics</td>
<td>Lindeman et al., 1995</td>
</tr>
<tr>
<td>Resistance exercise</td>
<td>4</td>
<td>DM</td>
<td>20 month training program; 4x per week; whole body resistance training</td>
<td>Not stated</td>
<td>All</td>
<td>Maximal elbow flexion strength unchanged; maximal knee extension force increased 100%</td>
<td>Milner-Brown and Miller 1988</td>
</tr>
</tbody>
</table>

6MWT = 6 minute walk test; DM = myotonic dystrophy; DM1 = myotonic dystrophy type 1; ECG = electrocardiogram; MHR = maximal heart rate; RM = repetition max.
• Decreased myopathy
• Enhanced sarcolemma structural integrity
• Increased force production

https://mc06.manuscriptcentral.com/apnm-pubs
Exercise + SMA

Increased FL-SMN mRNA

Increased FL-SMN protein

Improved NMJ biology

Preservation of αMN number

• Absence of muscle damage
• Improved muscle strength
• Enhanced motor function
• Prolonged survival
Exercise + DM1

AMPK

Decreased CUG foci
MBNL1 liberation

Corrective splicing

INSR

Troponin T2

SERCA

CIC-1

Enhanced expression of CIC-1 proteins

- Healthy muscle contraction and relaxation
- Diminished myopathy