Literature Review

# Physical Activity, Health Impairments, and Disability in Neuromuscular Disease

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## ABSTRACT

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Reduced physical activity is a consequence of progressive neuromuscular diseases, which negatively impacts quality of life and health outcomes. Reduced functional muscle mass is common to all neuromuscular diseases and results from both atrophy of disuse secondary to a sedentary lifestyle and muscle degeneration secondary to the disease itself. This review summarizes current concepts relating to the impact of reduced physical activity on health and fitness, potential determinants of physical activity levels in neuromuscular diseases, and new approaches to the quantitative measurement of physical activity in neuromuscular disease populations. The interrelationship of disease pathophysiology, impairment, functional limitation, disability, and societal limitation in the determination of physical activity in the community in neuromuscular diseases is discussed using Duchenne muscular dystrophy as an example. Future research pertaining to physical activity in neuromuscular disease will need to focus on the development of scientifically based recommendations concerning optimal exercise approaches with both disease-specific and general guidelines.

**Key Words:** Functional Muscle Mass, Exercise Rehabilitation, Deconditioning, Muscular Dystrophy

Neuromuscular diseases (NMD) are restricted to hereditary and acquired diseases of the peripheral neuromuscular system, including those affecting anterior horn cells, peripheral nerves, neuromuscular junctions, and muscle. The estimated total prevalence of the most common NMD conditions in the United States is 400,000.[1] The total prevalence approaches 4,000,000 if diabetes-related peripheral neuropathies and other acquired peripheral nerve disorders are included. Life satisfaction and health-related quality of life of people with NMD were reported by Abresch et al.[2] in a comprehensive quality-of-life survey comprising 811 individuals with NMD. The self-reported impacts of NMD on functional capacity and level of physical activity were also tabulated from these data and are shown in Tables 1 and 2. Common problems that reduce functional capacity, and hence quality of life, include weakness, fatigue, problems with locomotion, inability to exercise, pain, and problems with weight. The three problems most frequently cited as "very significant" by the NMD population—muscle weakness, difficulty exercising, and fatigue—all lead to reduced physical activity and a sedentary lifestyle.

This review summarizes current concepts relating to the impact of reduced physical activity on health and fitness, potential determinants of reduced neuromuscular function and physical activity levels in NMD, methodologic problems relating to the objective assessment of physical activity, and new approaches to the measurement of physical activity in people with NMD, particularly in pediatric populations. Future research pertaining to physical activity among people with NMD will need to focus on the development of scientifically based recommendations concerning optimal exercise guidelines and novel approaches to enhance levels of physical activity.[3]

## Physical Activity in Able-Bodied and Disabled Populations: Impact on Health and Fitness

Physical inactivity is enormously expensive in both human and economic terms. When the ability to be physically active and mobile is compromised, independence is lost,[4] and emotional well-being is reduced. A primary goal of many medical treatments and rehabilitation programs for disabled persons with NMD is to restore or maintain patients' ability to be physically active.

Improvement in physical fitness through increased physical activity has been shown to be important for health maintenance and disease prevention in able-bodied populations. Improvement in cardiopulmonary endurance, body composition, muscle strength and endurance, and flexibility are associated with reductions of risk factors associated with various degenerative diseases. Epidemiologic studies in adults suggest that regular physical activity contributes to longevity and decreases the risk of death from a variety of causes.[5,6] With respect to cardiovascular heart disease, inactivity has been shown to be the second most costly risk factor.[7] Physical activity is associated most strongly with the prevention and control of coronary artery disease,[8] hypertension,[9,10] non–insulin-dependent diabetes mellitus,[11] osteoporosis,[12,13] obesity,[14] and mental health problems.[15,16] In recent years, the Centers for Disease Control and Prevention and the American College of Sports Medicine,[17] the United States Public Health Service,[18] the National Institutes of Health,[19] and the United States Department of Health and Human Services[20] have published recommendations for increased physical activity based on health concerns.

People disabled by physical impairments as a result of NMD may in particular be at long-term risk for coronary artery disease, obesity, osteoporosis, anxiety, and depression.[21–27] In addition to general health benefits and disease prevention, improved physical activity may provide a number of disease-specific benefits to people with cardiac, pulmonary, and musculoskeletal impairments. In addition, improved physical activity is likely to contribute directly to improved community locomotion and community integration and to improved ability to participate in a variety of recreational activities.

Patterns of physical activity observed in childhood persist into adulthood and seem, in part, to determine adult levels of physical activity.[28,29] The Allied Dunbar National Survey of Fitness and Physical Activity,[30] in which 600 people participated, demonstrated that childhood activity was associated with the gen-

**TABLE 1**
*Problems that impact the quality of life of persons with slowly progressive neuromuscular diseases (N = 811)[a]*

| Rate the Difficulty You Have with the Following | Very Significant, % | Moderately Significant, % | Slightly Significant, % | Not a Problem, % |
|---|---|---|---|---|
| Difficulty with muscle weakness | 57 | 26 | 12 | 6 |
| Difficulty with fatigue | 40 | 31 | 22 | 8 |
| Difficulty getting exercise | 43 | 23 | 18 | 16 |
| Difficulty controlling weight | 18 | 18 | 28 | 36 |

[a] Data from personal communication. These findings were taken from neuromuscular disease survey data not previously reported by R. T. Abresch and colleagues.

**TABLE 2**
*Limitations on physical activity in persons with slowly progressive neuromuscular diseases (n = 811)*[a]

| How Much Does Your Health Limit You in the Following Activities? (from SF-36) | A Lot, % | A Little, % | Not at All, % |
|---|---|---|---|
| Vigorous activities such as running? | 93 | 3 | 4 |
| Walking more than a mile? | 84 | 9 | 7 |
| Walking several blocks? | 73 | 17 | 10 |
| Moderate activities such as pushing a vacuum cleaner? | 66 | 26 | 8 |
| Walking one block? | 54 | 27 | 18 |

[a] These findings were recalculated from physical activity data from the SF-36 survey conducted by Abresch et al.[2]

eral level of physical activity in adulthood. Thus, improved physical activity in childhood may have lasting health benefits in individuals with slowly progressive NMD.

## Health Consequences of Severe Muscle Disuse, Deconditioning, and Age-Related Muscle Wasting in Able-Bodied People

Individuals with NMD represent a very sedentary and deconditioned population. Their physical response to exercise testing is similar to that reported in poorly conditioned able-bodied subjects. When compared with conditioned individuals, poorly conditioned able-bodied subjects have lower work capacity (lower peak oxygen consumption)[31] associated with impairment in cardiopulmonary factors (lower peak oxygen consumption, ventilation, stroke volume, heart rate, and cardiac output and higher heart rate and oxygen consumption at defined submaximal workloads);[31–38] hypovolemia (reduced plasma, red cell, and total blood volumes) and negative water balance (decreased fluid intake relative to urinary output);[39–41] decreased orthostatic tolerance;[42] resting metabolic changes; body composition changes such as decreased lean body mass, increased fat mass, decreased muscle thickness and volume, and reduced bone mineral density;[43–49] decreased muscle strength and endurance;[42,44,45] thermoregulatory changes;[50,51] impaired limb proprioception;[52] impaired immune response and function;[46] and alterations in mood and neuropsychological performance.[53]

Many of these findings reported in bed-rest subjects have also been reported in aging subjects. In both sexes, a large portion of the age-associated decline in $VO_{2max}$ in non–endurance-trained individuals can be explained by the loss of muscle mass, which is observed with advancing age.[54,55] A difference also exists in the age-related rate of decline in $VO_{2max}$ between sedentary and active individuals, with the decline greater in sedentary individuals regardless of age.[56] In able-bodied adults, there is an age-related decrease in muscle mass (sarcopenia), an increase in body fat, and a concomitant decrease in strength.[57–64] The decrease in both muscle mass and strength with age is associated with functional impairments in both functional skills and physical activity. In the elderly, walking speed has been shown to be linearly associated with knee extensor strength over a large range of strength values.[60,65,66] Buchner et al.[67] recently documented a curvilinear relationship between leg strength and gait speed in the elderly. Thus, in some individuals, a seemingly small change in muscle function could lead to a large improvement in walking speed up to a certain level, above which improvements in strength may not significantly affect gait speed. Lower limb knee extensor power in the aged has been shown to be significantly related to habitual walking speed, ability to rise from a chair, and ability to climb stairs.[65,68]

It is likely, therefore, that the reduction in functional muscle mass in individuals with NMD and the associated functional impairments are the result of both atrophy of disuse secondary to a sedentary life style and muscle degeneration secondary to the disease. This reduction of functional muscle mass likely results in further reduction in activity levels among persons with NMD. To the extent that reduced exercise performance is due to the effects of detraining from a sedentary lifestyle, endurance exercise may be helpful to reverse the negative effects of the deconditioned state.[69]

## Objective Assessment of Physical Activity: Problems with Current Methods

Studies focusing on the relationship of physical activity to health and fitness have used a variety of objective methods for physical activity assessment. Although the methods all provide different information concerning levels of physical activity, all the methods have limitations. In addition, the applicability of the methods to pediatric populations varies. The most commonly employed methods are listed in Table 3.

Keeping a diary or log of daily activities, which relies on self-reported physical activity, has been shown to be inaccurate in children, largely because younger children lack the cognitive ability to recall details about their activity patterns. It has been shown that children can recall only 55–65% of their daily activities.[70] In another study, 11- to 13-yr-old children were able to recall only

**TABLE 3**
*Physical activity assessment methods*

| Method | Variable Measured | Major Limitations |
|---|---|---|
| Diary/daily log | Estimate of time spent at various activities | • Unreliable in children<br>• Not readily quantified |
| Doubly labeled water | Total energy expenditure over block of time | • High cost<br>• Complexity of procedure in studies of large populations<br>• Provides no information on frequency, intensity, or duration of physical activity |
| Pedometry | Total steps taken or distance traveled over a block of time | • Inaccurate at slow walking<br>• Unproven for those with gait anomalies<br>• Provides no information on frequency, intensity of duration of physical activity |
| Accelerometry | Two- or three-dimensional acceleration of an individual in specified time increments | • Units of measurement not well defined in terms of physical activity<br>• Influenced by passive movement of subject |
| Heart rate monitoring | Average heart rate over specified time increments | • Labor intensive to analyze<br>• Data are heavily influenced by factors other than physical activity |

46% of observed activities from the previous 7 days.

Doubly labeled water is a method that can assess energy expenditure and global physical activity levels in a subject in situ, but the main drawback is the cost, logistical complexity of handling saliva or urine samples, and the lack of information about the frequency, intensity, and duration of physical activity. Doubly labeled water provides estimates of total daily energy expenditure based on a number of assumptions. Validation of this technique has been performed in healthy able-bodied populations but not NMD populations.

Pedometry has been used to measure physical activity levels, but commercially available pedometers are generally very inaccurate, particularly at slow walking speeds.[71–73] This is relevant when considering the use of these devices in a disabled population with gait disorders.[74] In addition, available pedometers provide information regarding total steps or distance traveled, but no minute-to-minute information regarding the frequency, duration, or intensity of activity.

Accelerometers, including the Caltrac, Tri-Trac3D, Large Scale Integrated Activity Monitor, and the Actigraph, have been used recently to quantitatively measure physical activity. These devices are worn on the waist and record simple, incremental two- and three-dimensional accelerations over given time periods. However, the instruments are problematic for clinical applications because the units of measurement are not well defined with respect to a specific event of clinical interest. Thus, it is difficult to relate the data to recognizable activities, such as slow walking, comfortable walking, brisk walking, or running. In addition, passive movement (e.g., riding in an automobile or coasting downhill on a bicycle) influences the data acquisition. Tryon[75] prefaces his extensive summary of equipment used for measuring activity with the assertion that defining a basic unit of measure is critical to understanding any phenomenon under study. In the discussion of existing instruments used for ambulatory monitoring, he contends, "It can be argued that the step is the preferred unit of measure [for activity monitoring] because it is a natural unit of ambulation."

Long-term heart rate monitoring has been shown to be a useful measure of physical activity;[76,77] however, this method is labor intensive. It requires the acquisition of a heart rate–$VO_2$ calibration curve along with measurement of resting energy expenditure by indirect calorimetry for the calculation of both total energy expenditure and the physical activity index. This makes the technique impractical for larger clinical studies. In addition, at low heart rates, other confounding variables are introduced. Emotional stress will significantly elevate heart rate independent of any change in $VO_2$. Fitness levels also impact heart rate independent of actual levels of physical activity during a testing period.[78]

### Need for Objective, Continuous Physical Activity Monitoring Among Disabled Persons as a Functional Outcome Measure After Treatment to Improve Mobility

Mobility proficiency and degree of physical activity or community locomotion are important measures of functional status and outcome in persons with physical impairment due to

NMD. The functional mobility of these disabled populations can be evaluated and expressed in terms of what the disabled individual is capable of doing over brief time intervals using objective and standardized testing protocols in laboratory settings. Alternatively, functional mobility status may be based on what the disabled person actually does over extended periods in his or her own real-world community.

This approach was originally advocated by Halstead[79] as a complimentary functional outcome measure to traditional objective assessments of physical performance and physical capacity performed over brief evaluation periods, which are usually conducted in the laboratory, hospital, or clinic. The evaluation of both the biomechanics of gait and physical performance has progressed tremendously over the past decade, with elegant and objective studies elucidating the dynamic electromyographic profiles of lower limb muscles, kinematics, kinetics, and exercise physiology of locomotion in laboratory settings. However, assessments concerning what persons actually do in their own community over extended periods of time have largely been qualitative in nature.

There is a need for development of a technique to quantitatively and reliably measure the actual or "real-world" physical activity of disabled persons continuously over an extended period of time, in an unobtrusive manner. Objective measures of physical activity are important functional outcome measures in mobility-impaired populations. Currently, objective measures of actual physical activity are lacking and too frequently rely on patient or parental reports of physical activity levels or, alternatively, subjective impressions by clinicians. For example, measured distances traveled by physician-determined "community ambulators" may never exceed one city block among some disabled children.[80,81] Such children have been labeled community ambulators, despite the fact that the majority of their day is spent using a wheelchair.

Ideally, objective information regarding physical activity patterns in disabled and nondisabled subjects would include precise quantitative information regarding the following: (1) measures of when, during a given day or series of days, individuals are engaged in physical activity or community locomotion and when they are sedentary; (2) the intensity of the activity; (3) the average total daily physical activity occurring over an extended sample time of several days to weeks; and (4) the mean proportion of time spent at various investigator-defined physical activity intensities. An easily applied activity monitoring device, which could give objective assessments of patterns of physical activity in the real-world community over extended time periods, could become an extremely meaningful and valuable outcome tool to assess the impact of therapeutic interventions (medical treatments, orthopedic surgeries, new prosthetics or orthotics, and therapeutic exercise) on mobility.

The Prosthetics Research Study has recently developed a useful, objective approach that entails monitoring a simple event (steps) over much longer periods of time with an unobtrusive instrument. The Step Activity Monitor (SAM)[82–90] is small, self-contained, and worn on the ankle. The SAM detects steps (or gait cycles) with a high degree of accuracy and stores step counts in adjustable, regular time intervals (normally each minute) for a month or more at a time. The SAM provides a detailed minute-to-minute quantitative profile of physical activity. Data are provided regarding total steps per day, total steps at investigator-defined step activity levels, and minutes per day at investigator-defined intensities of step activity. A limitation of the SAM is the lack of information obtained regarding upper limb activity or activity that does not involve walking or running.

## Objective, Quantitative Measures of Physical Activity in NMD Populations

One of the few studies utilizing objective quantitative measures of physical activity in NMD populations was conducted by McCrory et al.[91] at the University of California–Davis. They utilized community-based ambulatory heart rate monitoring to measure energy expenditure in physical activity in 26 adult subjects with various NMD (myotonic muscular dystrophy, hereditary motor sensory neuropathy type 1, limb-girdle muscular dystrophy, fascioscapulohumeral muscular dystrophy, Becker muscular dystrophy, and spinal muscular atrophy type III). Energy expenditure in physical activity was determined by subtracting resting energy expenditure from total daily energy expenditure.

Energy expenditure in physical activity was significantly lower in NMD subjects than in control subjects and significantly lower in women than in men. This sex difference disappeared when energy expenditure in physical activity was adjusted for fat-free mass. The total daily energy expenditure of women with NMD was 35% less than that of control women. Likewise, the total daily energy expenditure of men with NMD was 20% less than that of control males. NMD women spent 74 ± 45 min/day with heart rate in the "active" range, compared with 206 ± 110 min/day for control women. Similarly, men with NMD spent 126 ±106 min/day and control men spent 248 ± 127 min/day with heart rate in the active range. NMD subjects also reported exercise at lower intensity levels than did control subjects. Body fat in NMD subjects was inversely related to the duration of exercise and fat-free mass.[91]

In another study, we used the

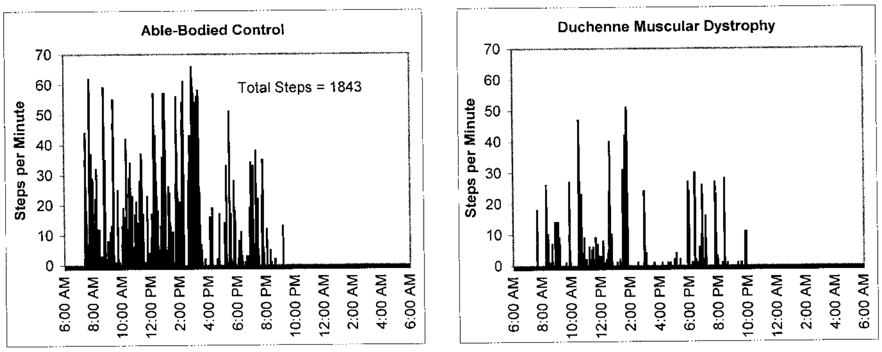

**Figure 1:** Stepwatch Step Activity Monitor profile for a continuous 24-hr step count in (*left*) an 11-yr-old boy, able-bodied control and (*right*) a 12-yr-old boy with Duchenne muscular dystrophy.

SAM to quantitatively measure physical activity in boys with Duchenne muscular dystrophy (DMD).[92] Participants were 16 ambulatory boys with DMD, aged 5–13 yr. The control group consisted of an age-controlled convenience sample of 21 able-bodied boys, aged 5–13 yr. Participants wore the SAM on the right ankle for three full days. The monitor recorded right steps or complete gait cycles. For the 3-day monitoring period, the steps were recorded continuously and stored as total right steps per consecutive 1-min blocks. Figure 1 shows a 1-day sample of step activity data for an able-bodied control subject and a boy with DMD. Data were analyzed to determine the time each subject spent at a low activity level (1–15 steps/min), a medium activity level (16–30 steps/min), and a high activity level (>30 steps/min). Low activity level includes sedentary tasks with intermittent periods of walking during activities, such as playing video games, eating, and class time. Medium activity level is moderate or intermittent walking or activity. High activity level is continuous walking or running for a minimum of 1 min. Each day, boys with DMD spent 40% fewer minutes than did controls at a high activity level. The DMD subjects spent a greater proportion of time each day in the inactive or sedentary range and the low-activity range as compared with age-matched controls. The boys with DMD also took significantly fewer steps per day at a high activity level (4456 ± 513 steps) than did controls (6311 ± 493 steps). These findings show that boys with DMD had a marked decrease in high levels of physical activity at a young age. This study illustrates the usefulness of the SAM as an objective tool for measuring frequency, duration, and intensity of physical activity and in quantitative outcome measures of disease progression and community mobility.

## Interrelationship of Factors Contributing to Reduced Physical Activity in Persons with NMDs

Multiple factors contribute to reduced physical activity in persons with NMD including loss of functional muscle tissue, muscle disuse, overuse injury, cardiopulmonary involvement, increased fat mass, contractures, reduced efficiency of locomotion (slower gait velocity and higher energy cost), reduced patient motivation, less social reinforcement for activity, increased depression, and increased societal barriers. The complexity of physical and social factors that accrue in a nonlinear way to create disability over highly variable time periods are aptly conceptualized in a model of the rehabilitation process developed by the National Center for Medical Rehabilitation Research.[3] An important part of communication among the members of the rehabilitation team is the use of a shared disability lexicon. Below, I have applied National Center for Medical Rehabilitation Research definitions for pathophysiology, impairment, functional limitation, disability, and societal limitation to DMD to illustrate the relationship between these factors and reduced physical activity and exercise capacity (Table 2).

***Pathophysiology.*** Pathophysiology is defined as "the interruption of or interference with normal physiologic and developmental processes or structures."[3] An example would be a gene deletion at the xp21 locus leading to the absence of dystrophin in DMD, which in turn leads to muscle membrane susceptibility to injury. Fibers undergo cycles of degeneration and regeneration until the regenerative capability ceases; the fiber undergoes irreversible necrosis and is replaced by fat and connective tissue. Thus, as a direct result of the underlying primary pathophysiology, there is a progressive loss of functional muscle fibers with muscle wasting, observed along with increased fat and collagen deposition. In addition, there is a concern that particular types of physical activity or exercise load may lead to "overwork weakness" and additional loss of muscle fibers. Kilmer summarizes evidence regarding overwork weakness in this issue (see "Response to Resistive Strengthening Exercise Training in Humans with Neuromuscular Disease" in this issue of the *American Journal of Physical Medicine and Rehabilitation*). Indirect measures of the pathophysiology involve analysis of muscle biopsy specimens for quantitative dystrophin analysis by Western blot, immunofluorescence stains for dystrophin, histopathological alterations, and ultrastructural changes by electron microscopy.

***Muscle Wasting and Body Composition Changes.*** Clinical measures of pathophysiology involve direct measures of muscle wasting and body composition changes. Muscle wasting is a hallmark of many NMD conditions. Focal and diffuse muscle wasting has been documented in subjects with DMD using computed tomography and magnetic resonance imaging. Both lean and fat tissue mass can be accurately and reliably estimated in children and adults over wide age ranges using dual-energy x-ray absorptiometry (DEXA).[64,95–98] DEXA is the only noninvasive body composition technique that gives regional estimation of lean mass, fat mass, and bone mineral content in each lower limb, each upper limb, and trunk. Two recent studies have demonstrated a significantly elevated fat/muscle ratio in subjects with myogenic atrophy,[99,100] and both functional activity scales and strength correlated closely with percentage of lean body mass measured by DEXA. Diffuse neurogenic atrophy is associated with decrease in the mass of all three compartments (lean mass, fat mass, and bone mineral content) but relatively normal fat/muscle ratios when standardized to body mass index. Thus, studies of regional body composition by DEXA could be used to monitor disease progression in such entities as muscular dystrophy or progressive denervating diseases such as amyotrophic lateral sclerosis, spinal muscular atrophy, and peripheral neuropathies.

Our group has had extensive experience measuring body composition, including fat-free mass and percentage of body fat in able-bodied and disabled adults and children using a variety of validated body composition measurement techniques.[101–110] Lean tissue deficits and increased adiposity in a series of 26 mildly affected adults with slowly progressive NMD[91] were recently documented by our group using air displacement body plethysmography.[107]

The mean percentage of total body fat by DEXA in a series of 16 ambulatory children with muscular dystrophy from our center was 26% higher than that observed in controls. Also, the ratio of thigh lean tissue in grams to body weight was 25% lower in DMD than in age-matched controls. In DMD subjects, the correlation between percentage of body fat by DEXA and quantitative levels of physical activity in the community measured by the SAM was $-0.61$ ($P < 0.05$).[92] It can be concluded that lean tissue deficits in patients with NMD are directly associated with reductions in physical activity due to concomitant impairments in strength, fatigue, cardiopulmonary function, increased energy cost of locomotion, and possibly contractures. The temporal sequence and causal direction between NMD-induced atrophy, sedentary activity, and disuse atrophy is often not clear and bi-directional.

*Impairment.* Impairment is defined as "a loss or abnormality at the organ or organ system level of the body."[3] An example is decreased strength in DMD due to loss of muscle fiber, impaired contractility, or disuse weakness. Other impairments include fatigue, reduced cardiopulmonary function, contractures, and excessive weight gain, caused in part by a reduction in physical activity.

*Relationship of Strength to Mobility in DMD.* We have published a number of studies utilizing static and isokinetic quantitative strength testing as a measure of impaired strength in disabled children and adults with neuromuscular disorders such as DMD.[102,104–106,111–116] Quantitative strength testing is a more sensitive measure of weakness than clinical examination, particularly when strength is grade 4–5 on manual muscle testing.[103,113] For example, Figure 2 presents data on quantitative isometric knee extension strength as a percentage of control, and manual muscle testing results, for 15 DMD subjects and 22 controls. At age 6, the reduction in tension developed by knee extensors of DMD subjects was approximately 50% of control values for knee extension, whereas knee extension was between grade 4 and 5 on clinical manual muscle testing.

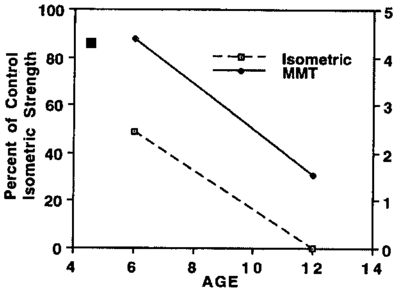

**Figure 2:** Isometric knee extension strength as a percentage of normal control values *vs.* age (*dashed line* regression) and corresponding knee extension manual muscle testing score *vs.* age (*solid line* regression) in subjects with Duchenne muscular dystrophy. Reproduced with permission from McDonald et al.[103]

Lower limb strength remains as one of the most important factors influencing whether subjects with disability attain functional ambulation.[103,117] There is a close relationship between specific knee extension strength and mobility status in DMD.[103] Loss of ambulation was shown to occur in boys with less than antigravity quadriceps strength. The Spearman rank-order correlation between knee extension strength by manual muscle testing and gait velocity in 31 DMD subjects was 0.667 ($P = 0.000$) in our series. Gait velocity was found to be a strong predictor of time to a wheelchair in 51 DMD subjects; 89% of boys who walked 10 m in <6 sec were more than 2 yr to a wheelchair, and 100% of subjects who walked 10 m in ≥12 sec were less than 1 yr to a wheelchair ($P = 0.001$).[103]

*Disuse Weakness in DMD.* Disuse of muscle fibers in able-bodied individuals results in reduced muscle fiber size, decreased fiber cross-sectional area, lower force production, and reduced muscle endurance.[118] Although there is no direct evidence that demonstrates an association between muscle disuse and reduced physical activity in persons with NMD, studies examining aerobic fitness, total daily energy expenditure, and physical activity levels suggest that persons with slowly progressive NMD are sedentary and poorly conditioned.[38,91] In addition, in more rapidly progressive NMD such as DMD, short periods of bed rest result in significant loss of strength and function that may not be reversible.[119] Thus, it is likely that disuse results in significant negative consequences to the child with DMD, and these deleterious effects may lead to further reductions in physical activity and further disuse.

***Relationship of Fatigue to Physical Activity in DMD.*** Although our extensive survey showed that muscle weakness, difficulty getting exercise, and fatigue are among the most significant factors negatively influencing quality of life in persons with NMD, the relationship between fatigue and physical activity in the NMD population has received little study to date. This is partly due to inherent difficulties with the objective study of fatigue, namely difficulties in study design and the effort-dependent nature of the protocols. In addition, the complex relationship between primary fatigue from the NMD and secondary fatigue due to disuse must be considered.[120]

If muscles that function as the prime movers of a joint are weak, we assume that they are forced to contract at a higher percentage of their maximal strength to perform the same activity as muscles in able-bodied individuals.[121] This will shorten the time it takes for muscle to fatigue and is undoubtedly one of the sources of fatigue in patients with significant loss of muscle strength. One study by Sharma et al.[122] focused on fatigue in DMD using a 4-min sustained voluntary contraction of the tibialis anterior. They found no difference between control and DMD subjects in intramuscular fatigue (the decline in tetanic force during a 4-min maximum sustained voluntary contraction) and excitation-contraction coupling.[122] Miller summarizes the human literature pertaining to fatigue in NMD in this issue the *American Journal of Physical Medicine and Rehabilitation* ("Role of Fatigue in Limiting Physical Activities in Humans with Neuromuscular Diseases").

***Cardiopulmonary Involvement and Physical Activity in DMD.*** The dystrophin protein is absent in both the myocardium and the cardiac Purkinje fibers in patients with DMD. Presence of cardiomyopathy affects the response to cardiopulmonary exercise in ambulatory children with DMD. In DMD, the myocardial impairment remains clinically silent until late in the course of the disease, possibly due to reduced physical activity. Cardiomyopathy and restrictive pulmonary disease are likely to have a greater impact on physical activity in more slowly progressive NMD.

The ability to evaluate impaired capacity of the cardiopulmonary system in NMD patients with mobility impairments has recently been improved by the development of portable metabolic carts, which transmit data regarding heart rate, ventilation, oxygen uptake, carbon dioxide production, and caloric expenditure by indirect calorimetry. Using the $K4b^2$ portable metabolic cart (COSMED, Rome, Italy), we recently demonstrated that DMD subjects have a diminished cardiopulmonary reserve, as evidenced by a significantly lower maximal heart rate (150 ± 15 beats/min) than controls (183 ± 15 beats/min), and DMD subjects had a lower peak $VO_2$/kg body weight (25.6 ± 9.5 ml/kg) than controls (36.8 ± 10.3 ml/kg). At rest, DMD subjects maintain a resting tachycardia to compensate for a reduced cardiac stroke volume. Few human studies have focused on adaptations and responses to cardiopulmonary exercise in NMD, and this will likely be an increasing research priority, particularly in light of animal studies demonstrating benefits of aerobic exercise protocols in dystrophin-deficient muscle.

***Contractures in DMD.*** Significant joint contractures have been found in nearly all DMD children older than age 13 and are a direct result of reduced standing and physical activity. The presence of lower limb contractures in DMD boys is strongly related to onset of wheelchair reliance.[103] Hip and knee flexion contractures are rare in DMD children while they are predominantly ambulatory, but they develop soon after they assume a sitting position in a wheelchair for most of the day. The lack of lower limb weight bearing likely contributes to the rapid occurrence of ankle plantarflexor contractures after transition to a wheelchair. Given the tremendous replacement of muscle by fibrotic tissue in DMD subjects, it is not surprising that a muscle with less than antigravity extension strength, statically positioned in flexion, develops a flexion contracture subsequent to wheelchair reliance.

***Weight Gain in DMD.*** Obesity is a substantial problem for DMD children immediately after the loss of independent ambulation,[103,123,124] This is likely due to a reduction in total daily activity-associated energy expenditure with unchanged caloric intake.

***Functional Limitation.*** Functional limitation is defined by the National Center for Medical Rehabilitation Research as "restriction or lack of ability to perform an action in the manner or within the range consistent with the purpose of an organ or organ system."[3] An example would be decreased velocity of ambulation or decreased distance achieved per unit time.

DMD boys ambulate with a slower self-selected walking speed than age- and sex-matched controls.[125] Our group has recently evaluated the energy cost of locomotion in boys with DMD measured with a portable metabolic cart.[125] Participants were 14 ambulatory boys with DMD, aged 5–16 yr (9.9 ± 2.7 yr). The control group consisted of a convenience sample of 17 able-bodied boys, aged 6–16 yr (9.3 ± 2.6 yr). Subjects were evaluated lying, sitting, standing, and ambulating for 10 min at a comfortable walking speed. All controls and 12 boys with DMD also ran a 100-m sprint. Data were analyzed to determine the metabolic efficiency of locomotion by the calculation of oxygen cost (ml oxygen/kg/m). Boys with DMD walked a significantly shorter distance over 10 min (437 ± 178 m) than did controls (774 ± 69 m). Boys with DMD had a significantly higher ambulating oxygen cost (0.42 ± 0.40 liters oxygen/kg/m) than controls (0.21 ± 0.05 liters oxygen/kg/m) and a lower $VO_2$/kg (12.9 ± 3.0 ml/kg) than controls (16.6 ± 4.0 ml/kg). Boys with DMD sprinted significantly slower (96 ± 49 m/min) than did controls (248 ± 23 m/min), and the DMD subjects had a significantly higher sprinting oxygen cost (0.19 ± 0.09 liters oxygen/kg/m) than controls (0.08 ± 0.03 liters oxygen/kg/m). In conclusion, these results show that boys with DMD experience functional limitation as evidenced by decreased metabolic economy of movement (higher oxygen cost) during walking and running, lower oxygen uptake during comfortable movement and running, and reduced velocities of walking and running. Whereas changes in oxygen uptake or reduced peak aerobic capacity may be examples of impairments, the reduced economy of movement during walking or running is a functional limitation.

*Disability.* Disability is defined by the National Center for Medical Rehabilitation Research as "a limitation in performing tasks, activities, and roles to levels expected within physical and social contexts."[3] An example would be the inability to exercise or decreased daily physical activity in the community as a result of DMD.

As described above, we have recently investigated the impairments and functional limitations of young, ambulatory boys with DMD before their full-time wheelchair use. We can now examine the interrelationships between impairment, functional limitation, and disability by correlating clinical measures of body composition, strength, and function with quantitative measures of daily physical activity. Disability, as determined by daily community ambulation using the SAM, seems to be related to the degree of impairment and functional limitation. Reduction in self-selected walking speed and knee extension strength were significantly correlated with reduction in total step activity in the community. In another study, obesity was associated with decreased daily activity as measured by the SAM.[126] Step activity monitoring provides continuous, time-based daily physical activity data during real-world community activity, and thus, it is a useful quantitative community-based disability measure. Further studies are needed to better understand the degree and relative impact of these impairments and functional limitations on disability.

*Societal Limitation.* Societal limitation is defined by the National Center for Medical Rehabilitation Research as "restrictions attributable to social policy or barriers (structural or attitudinal) which limit fulfillment of roles or deny access to services and opportunities associated with full participation in society."[3] An example would be a young teenager with DMD in a manual wheelchair who does not participate in his school's physical education program because adaptive physical education is either not available or poorly developed. Although societal limitations likely have a strong impact on physical activity patterns among NMD subjects, little research has focused on the relationship between such barriers and daily physical activity and exercise practices.

## SUMMARY

The three problems most frequently noted by the NMD population to be a "very significant problem"—muscle weakness, difficulty exercising, and fatigue—all lead to reduced physical activity and an increasingly sedentary existence. Individuals with NMD represent a very sedentary and deconditioned population, and they may be at particular long-term risk for coronary artery disease, obesity, osteoporosis, anxiety, and depression.[22–27] In addition to general health benefits, improved physical activity in this population may provide a number of disease-specific benefits due to direct effects on cardiac, pulmonary, and musculoskeletal impairments. It is likely that the reduction in muscle mass in individuals with NMD and associated impairments (strength decrements) and functional limitations (slow walking speed) are secondary to both disuse secondary to a sedentary life style and muscle degeneration secondary to the disease. This reduction of functional muscle mass likely results in further reductions in activity levels among persons with NMD. To the extent that reduced exercise performance is due to the effects of detraining from a sedentary existence, endurance exercise may be helpful in reversing the negative effects of the deconditioned state. In addition, improved physical activity in persons with NMD through exercise or other therapeutic approaches such as pharmacologic treatment is likely to contribute directly to improved community locomotion and community integration.

Future research evaluating physical activity in NMD will need to focus on the development of scientifically based recommendations concerning optimal exercise guidelines including (1) disease-specific recommendations related to types of exercise that can be safely performed, (2) recommendations regarding the minimum frequency, intensity, amount, and duration of exercise required to produce beneficial effects, and (3) the development of novel approaches to enhance levels of physical activity in persons with varied severity of impairment due to NMD.

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