REGIONAL BODY COMPOSITION AND FUNCTIONAL IMPAIRMENT IN PATIENTS WITH MYOTONIC DYSTROPHY

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Accepted 7 March 2011

ABSTRACT: Introduction: In this study we determined regional body composition in myotonic dystrophy (DM1) and able-bodied controls and evaluated the relationship between fat and lean tissue mass and functional impairment in DM1 patients. Methods: Dual-energy X-ray absorptiometry (DEXA) was used to obtain regional measurements of fat-free mass index (FFMI) and fat mass index (FMI) in 48 DM1 and anthropometrically matched control pairs. Results: DM1 patients had lower regional FFMI and higher FMI than controls (P < 0.01–0.001). In DM1 patients, total FMI increased significantly with increased muscular disability rating, decreased motor function measurement, and with both decreasing vital capacity and total lung capacity. Hypertriglyceridemia correlated with increasing FMI. Conclusions: Regional FFMI is decreased in DM1, whereas FMI is underestimated by body mass index and is negatively correlated with patients’ functional capacity. DEXA may provide valuable supporting evidence in the management of DM1.

MUSCLE NERVE 000: 000–000, 2011

Myotonic dystrophy type 1 (DM1) is an autosomal dominant inherited disorder related to the expansion of a trinucleotide (CTG) repeat in the 3'-untranslated region of the myotonic dystrophy protein kinase gene (DMPK).1 Clinical features in DM1 are progressive muscle weakness and atrophy, myotonia, and involvement of the central nervous system, eyes, heart (cardiomyopathy, intracardiac conduction defects), and endocrine system.2 Disease severity and age at onset are correlated with the expansion of the CTG repeats.2 Muscle involvement is characterized by slowly progressive, stereotyped, regional weakness, along with muscle wasting typically involving lip and eye closure, lid elevation, jaw muscles, and sternomastoid, whereas posterior neck and shoulder girdle muscles remain relatively preserved. Limb involvement is usually distal in the early stages of the disease.2

Muscle wasting contributes to strength impairment, diminished mobility, respiratory insufficiency, and decreased quality of life. Despite reduced muscle mass, a number of patients with neuromuscular disorders (NMDs) are overweight, and excess adiposity burdens mobility and compromises breathing. Moreover, it has been suggested that obesity in NMD patients leads to a high risk of developing chronic diseases.3 In fact, myotonic dystrophy is thought to be associated with features of the metabolic syndrome, including insulin resistance, increased body fat mass, and hypertriglyceridemia.4-6

Body mass index (BMI) has been widely used to screen for overweight in otherwise able-bodied subjects. However, it is not useful for fat mass assessment in NMD patients, because a higher fat/muscle ratio is found in myogenic atrophy due to fat infiltration into atrophied skeletal muscles.7 Thus, a quantitative assessment of both focal and generalized muscle wasting and adiposity would be a useful way to monitor the natural history of disease progression in DM1 patients. Dual-energy X-ray absorptiometry (DEXA) is a noninvasive body composition technique that provides regional estimations of fat-free mass (FFM) and fat mass (FM).8 It has been used successfully in the assessment of whole body and regional body composition in subjects with neuromuscular diseases.7,9,10 However, such studies have not been done in DM1 patients.

The goals of this study were to: (1) compare regional and whole body fat-mass index and fat-free mass index of DM1 patients with those of able-bodied controls; and (2) understand the relationship between whole body and regional body composition and functional muscular disability in DM1 patients.

METHODS

Patients. Fortyeight DM1 patients, aged 18–67 years, were recruited from a university-based neuromuscular department. The diagnosis of DM1 was confirmed by molecular genetic testing in all patients. These patients were matched with 48 gender-, age-, height-, and weight-matched, able-bodied controls, aged 17–67 years. The following criteria were used to match the subjects: age within 3 years; height within 2 cm; and weight within 3 kg. Height was measured in all subjects to the nearest 0.5 cm, and weight was determined to the nearest whole kg.
nearest 0.5 kg. Controls were screened from a large database of patients who underwent osteodensitometry with whole body and regional body measurements of fat-free and fat masses in an ongoing program of bone quality assessment at our university hospital. Myopathic patients and those treated by drugs with neuromuscular toxicity were excluded. Among the remaining patients, those who satisfied the aforementioned criteria were selected, and controls were randomly selected among them. Informed consent was obtained from patients and controls. Thus, there were 31 female and 17 male pairs.

Regional body composition was obtained by DEXA with fan-beam technology (QDR 4500A; Hologic, Inc.). A standardized procedure was used for positioning the patient and using the QDR software. All scans were performed and analyzed by a certified technician. For regional body composition measurements, the Hologic software readings divided the body into head, trunk, left and right entire arms, and left and right entire legs. The arm region was delineated by a vertical line passing through the shoulder joint, and the leg region was delineated by an oblique line passing through the femoral neck. The head region was delineated by a curved line drawn under the chin. The DEXA scans were analyzed with the Hologic software for body composition assessment using a three-compartment model of body composition: lean tissue mass (LTM); FM; and bone mineral content. Bone mineral content and LTM were added to obtain FFM for each region. Regional or whole body percent fat tissue mass was obtained by dividing FM by the sum (FM + FFM) for each region. Finally, all whole and regional body LTM, FFM, and FM values were normalized to height squared in order to calculate the lean tissue mass index (LTMI), fat-free mass index (FFMI), and fat mass index (FMI). By dividing LTM, FFM, and FM by height squared. Body mass index (BMI) was calculated by the formula: body weight (kg) divided by height squared (m²).

**Patients with Myotonic Dystrophy.** Disease severity was assessed using the muscular disability rating scale (MIRS), as described by Mathieu et al., and the motor function measurement (MFM) scale. Patients were divided into the five MIRS classes as follows: 1 = no clinical impairment; 2 = minimal signs of impairment; 3 = distal weakness; 4 = moderate proximal weakness; and 5 = nonambulatory. The MFM scale comprises 32 items in three dimensions: standing position and transfers (D1); axial and proximal motor function (D2); and distal motor function (D3). Total MFM scale (D1+D2+D3) data were also obtained. Total lung capacity and vital capacity were determined by plethysmography and expressed as percent of predictive value. Expansion of CTG repeats was measured on genomic DNA extracted from peripheral blood leukocytes using Southern blot analysis in which DNA was digested with BglI and EcoRI and probed with the DNA probe p5B1.4.

**Statistical Analysis.** Comparison of DM1 subjects with respective anthropometrically matched controls was performed using the paired Student t-test. Because of multiple statistical tests, only P values < 0.02 were considered significant. In other statistical analyses, categorical variables were compared using the chi-square test, and the relationship between two quantitative variables was studied by linear regression. Two-way analysis of variance and covariance analysis (ANCOVA) were used to compare qualitative and quantitative variables, respectively, taking into consideration the differences in body composition between males and females. P < 0.05 was considered significant.

**RESULTS**

**Demographics, Anthropometrics, and Body Composition Analysis.** Whole body and regional fat-free and fat masses were obtained from all DM1 patients and controls. Demographic and anthropometric data are presented in Table 1. BMI was > 25 kg/m² in 48% of DM1 patients. There was no significant difference between DM1 patients and controls for height, weight, and BMI. This allowed for assessment of any disparities in body composition with regard to FMI and FFMI.

DM1 patients exhibited significantly higher FMI and significantly lower FFMI than able-bodied controls (Table 2). Both the increase in FMI and the decrease in FFMI affected all regional segments in DM1 patients, aside from trunk FFMI and leg FMI (Table 2). The average increase in FMI was 1.57 ± 2.42 kg/m² in males and 0.93 ± 1.52 kg/m² in females. This increase in fat mass
was not statistically correlated with BMI, because FMI regression lines in DM1 patients and controls were parallel (Fig. 1). The average decrease in FFMI was 1.84 ± 2.19 kg/m² in males and 1.33 ± 1.38 kg/m² in females when compared with matched controls (Fig. 1). The relationship between age and whole body percent fat tissue mass was also examined. DM1 subjects had an increased percent fat mass with age regardless of gender ($P < 0.05$ by ANCOVA). In contrast, there was no significant change with age in the control group.

### General Characteristics of DM1 Patients.

The mean CTG repeat expansion was 731 ± 419 (range 70–1800) in DM1 patients and was not correlated with age. Eight patients (16.7%) were assigned MIRS = 1, 15 patients (31.3%) MIRS = 2, 12 patients (25.0%) MIRS = 3, 11 patients (22.9%) MIRS = 4, and 5 patients (10.4%) MIRS = 5. Eight DM1 patients (16.7%) presented with type 2 diabetes, and 22 patients (45.8%) had dyslipidemia, consisting of hypertriglyceridemia ($n = 13$) or both hypercholesterolemia and hypertriglyceridemia ($n = 9$).

### Regional Body Composition and Motor Function Assessment in DM1 Patients.

To further investigate regional body composition, the left and right values of arm and leg FMI and LTMI were averaged. Disease severity is known to be correlated with increased size of CTG repeat expansion. In this series, expanded CTG repeats correlated significantly with decreasing percent vital capacity ($r = -0.549; P < 0.001$), decreasing MFM scale ($r = -0.361; P = 0.01$), and increasing MIRS ($r = -0.332; P = 0.02$), but not with age ($r = -0.178; P = 0.25$). There was no significant relationship between expansion in CTG repeats and regional body composition data, except for percent arm and leg fat, which increased significantly, irrespective of gender ($P < 0.02$ each, ANCOVA).

### Table 2. Fat-free mass and fat mass normalized to height squared in patients with myotonic dystrophy and in matched controls.

<table>
<thead>
<tr>
<th>Body composition</th>
<th>DM1 patients ($n = 48$)</th>
<th>Controls ($n = 48$)</th>
<th>Paired Student t-test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fat-free mass index (kg/m²)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left arm</td>
<td>0.852 ± 0.211</td>
<td>1.001 ± 0.243</td>
<td>$P &lt; 0.0001$</td>
</tr>
<tr>
<td>Right arm</td>
<td>0.902 ± 0.242</td>
<td>1.037 ± 0.246</td>
<td>$P &lt; 0.0001$</td>
</tr>
<tr>
<td>Left leg</td>
<td>2.38 ± 0.52</td>
<td>2.91 ± 0.55</td>
<td>$P &lt; 0.0001$</td>
</tr>
<tr>
<td>Right leg</td>
<td>2.37 ± 0.52</td>
<td>2.84 ± 0.54</td>
<td>$P &lt; 0.0001$</td>
</tr>
<tr>
<td>Trunk</td>
<td>8.62 ± 1.48</td>
<td>8.75 ± 1.46</td>
<td>$P = 0.24$</td>
</tr>
<tr>
<td>Head</td>
<td>1.31 ± 0.17</td>
<td>1.38 ± 0.13</td>
<td>$P = 0.006$</td>
</tr>
<tr>
<td>Total</td>
<td>16.4 ± 2.8</td>
<td>18.0 ± 2.9</td>
<td>$P &lt; 0.0001$</td>
</tr>
<tr>
<td>Fat mass index (kg/m²)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left arm</td>
<td>0.686 ± 0.322</td>
<td>0.556 ± 0.296</td>
<td>$P &lt; 0.0001$</td>
</tr>
<tr>
<td>Right arm</td>
<td>0.687 ± 0.326</td>
<td>0.591 ± 0.316</td>
<td>$P = 0.0037$</td>
</tr>
<tr>
<td>Left leg</td>
<td>1.70 ± 0.63</td>
<td>1.55 ± 0.71</td>
<td>$P = 0.048$</td>
</tr>
<tr>
<td>Right leg</td>
<td>1.70 ± 0.62</td>
<td>1.60 ± 0.69</td>
<td>$P = 0.089$</td>
</tr>
<tr>
<td>Trunk</td>
<td>4.25 ± 2.11</td>
<td>3.67 ± 2.00</td>
<td>$P = 0.0012$</td>
</tr>
<tr>
<td>Head</td>
<td>0.398 ± 0.074</td>
<td>0.357 ± 0.041</td>
<td>$P &lt; 0.0002$</td>
</tr>
<tr>
<td>Total</td>
<td>9.44 ± 3.82</td>
<td>8.28 ± 3.81</td>
<td>$P &lt; 0.0001$</td>
</tr>
</tbody>
</table>

Statistical data obtained using paired Student t-test. P-values <0.02 (in bold) considered significant based on multiple comparisons.

**FIGURE 1.** Relationship between fat mass normalized to height squared and BMI (lower panels) and fat-free mass normalized to BMI (upper panels) in DM1 patients and matched controls.
The relationship between functional disability and body composition was first analyzed using MIRS in DM1 patients. Whole body fat mass index, as well as fat mass index in the leg, arm, and trunk, also increased with MIRS (Fig. 2), whereas BMI increased slightly, especially in women ($P < 0.02$, ANOVA). This was essentially due to an increase in fat in patients with MIRS 4 or 5. However, no significant decline in regional or whole body LTMI could be observed in DM1 patients.

Motor function measurement using the MFM scale was also compared with regional body composition. The MFM scale correlated negatively with age ($r = -0.390$; $P < 0.01$). It also showed a negative correlation with BMI ($r = -0.313$; $P < 0.05$). No relationship was found between regional or whole body FFMI and MFM score. However, total MFM score correlated negatively with whole body FMI ($r = -0.521$; $P < 0.001$; Fig. 3), arm FMI ($r = -0.594$; $P < 0.001$), leg FMI ($r = -0.598$; $P < 0.001$), and trunk FMI ($r = -0.587$; $P < 0.001$) by ANCOVA. In addition, multivariate analysis revealed that the decrease in total MFM score was independently linked to an increase in whole body FMI, to a decrease in whole body LTMI, and to gender. Similar results were obtained for the D1 score (standing position and transfers) (Fig. 3). D2 and D3 scores were also significantly correlated with arm and leg FMI but not with whole body FMI.

Percent vital capacity ($\%VC$), as expressed by percent predicted value, was negatively linked to MFM scale ($r = -0.636$; $P < 0.001$), MIRS ($r = -0.607$; $P < 0.001$), and BMI ($r = -0.300$; $P < 0.02$). Covariance analysis indicated that $\%VC$ decreased with increasing FMI ($r = -0.360$; $P < 0.001$) (Fig. 4) and increasing trunk FMI ($r = -0.375$; $P < 0.001$). Similar results were also observed with total lung capacity ($\%TLC$) (Fig. 4). However, neither FMI nor FFMI remained...
independent factors in multivariate analysis of %VC or %TLC including MIRS (or MFM scale) and gender, indicating that advancing disease severity was the main factor that explained decreasing lung volumes in DM1 patients.

Patients with MIRS 3–5 had more frequent hypertriglyceridemia \((P < 0.01)\) and type 2 diabetes \((P = 0.01)\). Hypertriglyceridemia patients exhibited higher whole body \((r = 0.381; P < 0.01)\) and trunk \((r = 0.446; P < 0.002)\) FMI and, to a lesser extent, higher arm \((r = 0.341; P < 0.02)\) and leg \((r = 0.390; P < 0.01)\) FMI than patients with normal triglyceridemia. Using multivariate analysis, trunk fat mass index and gender were independent factors explaining hypertriglyceridemia. All these results persisted in analyses restricted to DM1 patients who had a BMI of <25 kg/m². However, we did not find any significant body composition changes in type 2 diabetic DM1, even though trunk FMI and whole body FMI tended to increase in these patients \((P = 0.051 \) and \(P = 0.10\), respectively).

No significant relationship was found between regional or whole body LTMI and age, MIRS, muscle function, or metabolic variables.

**DISCUSSION**

In this study, significant differences were found in regional and whole body composition in DM1 patients when compared with anthropometrically matched controls. Of note, an increase in fat mass together with a concomitant decrease in fat-free mass was observed in all regional measurements, aside from the trunk. Such results have also been reported in other NMDs, such as dystrophinopathies, facioscapulohumeral dystrophy, spinal muscular atrophy, and amyotrophic lateral sclerosis.\(^{8,10,14–18}\)

Percent fat mass increased with increasing age in DM1 patients, as opposed to no significant change in matched controls. This could reflect the evolution of muscular involvement in DM1, with a progressive loss of muscle with fat infiltration. Likewise, arm and leg percent FM were positively correlated with increased expansion of CTG repeats. This could depict an additional aspect of disease severity in DM1 patients, which is thought to be correlated with expanded CTG repeats.\(^{2–5}\)

We also evaluated disease severity of DM1 patients with MIRS. Results revealed an increased fat mass index with increasing MIRS, a phenomenon particularly evident in patients with proximal weakness (categorized as MIRS 4 and 5). This increase in fat mass in the most severely affected patients was found in all regional measurements.

It is noteworthy that DM1 patients with higher fat indices had statistically significant worsening of their MIRS and muscle function. In keeping with this observation, we also found a significant correlation between decreasing MFM scale and increasing whole body and regional FMI in DM1 patients. In correlation with worsening disease severity, %VC as well as %TLC diminished as increasing trunk and whole body fat indices.

In contrast to fat mass indices, we did not find significant variation in lean tissue mass indices with muscle function. In addition to muscle mass, DEXA-assessed LTM is also comprised of non-muscle compartments, such as skin, connective tissue, and the fat-free portion of adipose tissue.\(^{19}\) Tissue water also interferes with lean tissue calculation. All these non-muscle compartments contribute significantly to the calculation of LTM, and lean tissue mass has been positively correlated with trunk adiposity.\(^{20}\) This may be further magnified in NMDs such as DM1. Indeed, as muscle tissue is gradually replaced by fibrosis and fat, the fibrotic tissue is still represented as lean tissue.

Insulin resistance is a classical feature of DM1\(^{21}\) and is related to altered splicing of insulin receptor transcripts.\(^{22}\) This leads to an increased expression of 11beta-hydroxysteroid dehydrogenase type 1 in adipose tissue and contributes to development of the metabolic syndrome without obesity.\(^{4,5}\) Hence, increased blood levels of leptin or adiponectin,\(^{21,23}\) both biological features of the metabolic syndrome, have recently been reported in DM1 patients, as well as a high frequency of non-alcoholic fatty liver disease, which is strongly associated with markers of insulin resistance.\(^{24}\) Although we did not study the criteria for the metabolic syndrome in this cohort of DM1 patients, hypertriglyceridemic DM1 patients exhibited higher whole body and regional fat mass indices than other DM1 patients, especially trunk fat mass. These abnormalities persisted when statistics were restricted to patients with normal BMI. This may suggest a relationship between fat redistribution and metabolic disturbances in DM1. In this way, abdominal obesity has been found to be linked to non-alcoholic fatty liver disease in DM1.\(^{24}\)

In DM1 patients, increased fat mass could be considered a reflection of fat involution in muscles. Because whole body and regional fat masses are correlated with disease severity, regional DEXA could therefore provide a useful secondary outcome measurement of disease progression in future clinical trials in addition to muscle strength and disability scores. Moreover, DM1 patients carry the additional risk of insulin resistance and subsequent metabolic risk factors, such as obesity due to sedentary lifestyle, reduced mobility, and resting energy expenditure, as shown in patients with other NMDs.\(^{3,16,17}\) Although our study was not
designed to determine the prevalence of obesity in the DM1 population, it is worth noting that overweight was found in about 50% of the DM1 patients in this study, whereas 25% could be considered obese according to the World Health Organization definition (BMI >30 kg/m²). Obesity aggravates handicap, and increased fat mass is an additional burden on already severely weakened muscles. This could possibly lead to decreased motor function and increased morbidity associated with the disease. However, BMI was initially developed for an able-bodied population and has been used as a rough indicator of body fat percentage. Our findings strongly suggests that BMI may not be an appropriate index of overweight or obesity for DM1 patients, as demonstrated in other study populations with neuromuscular disorders. Presently, it remains unknown whether achievement and maintenance of low fat composition improves or worsens motor function and outcome in DM1 remains. In an effort to reduce overweight in obese DM1 patients, further intervention studies could use DEXA measurements to test the effect of specific treatments, such as diet therapy, on regional fat composition and to correlate it with motor function.

In conclusion, these results highlight the abnormal fat distribution in DM1 patients and the relationships between regional fat measurements and disease severity. Thus, DEXA appears to be a cost-effective method that can be utilized to measure disease severity, and it may have a role as a secondary outcome measure in future clinical trials. Regional DEXA may also provide valuable support in nutritional management with the aim of preventing overweight in patients with DM1 and other neuromuscular disorders.

This work was presented as a poster at the XIIth International Congress on Neuromuscular Diseases, July 2010, Naples, Italy.

REFERENCES
