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ORIGINAL ARTICLE

Body composition analysis in patients with myotonic dystrophy types 1 and 2

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Abstract

Introduction To date, there are only several reports on body composition in myotonic dystrophy type 1 (DM1) and there are no data for myotonic dystrophy type 2 (DM2). The aim was to analyze body composition of patients with DM1 and DM2, and its association with socio-demographic and clinical features of the diseases.

Methods There were no statistical differences in sociodemographic features between 20 DM1 patients and 12 DM2 patients. Body composition was assessed by DEXA (dual-energy x-ray absorptiometry). A three-compartment model was used: bone mineral content (BMC), fat mass (FM), and lean tissue mass (LTM).

Results Patients with DM1 and DM2 had similar total body mass (TBM), BMC, FM, and LTM. Patients with DM1 had higher trunk-limb fat index (TLFI) in comparison to DM2 patients which indicates visceral fat deposition in DM1 (1.16 ± 0.32 for DM1 vs. 0.87 ± 0.23 for DM2, $p < 0.05$). Right ribs bone mineral density was lower in DM2 group (0.68 ± 0.07 g/cm^2 vs. 0.61 ± 0.09 g/cm^2, $p < 0.05$). Higher percentage of FM in legs showed correlation with lower strength of the upper leg muscles in DM1 ($\rho = -0.47$, $p < 0.05$). Higher muscle strength in DM2 patients was in correlation with higher bone mineral density ($\rho = +0.62$, $p < 0.05$ for upper arm muscles, $\rho = +0.87$, $p < 0.01$ for lower arm muscles, $\rho = +0.72$, $p < 0.05$ for lower leg muscles).

Conclusion DM1 patients had visceral obesity, and percentage of FM correlated with a degree of muscle weakness in upper legs. In DM2 patients, degree of muscle weakness was in correlation with higher FM index and lower bone mineral density.

Keywords Myotonic dystrophy type 1 · Myotonic dystrophy type 2 · Body composition · Visceral obesity · Bone mineral density · Muscle weakness

Introduction

Myotonic dystrophies are hereditary, slowly progressive, multisystemic disorders. Although there are certain etiopathogenic similarities between DM1 and DM2, significant differences in the clinical presentations are observed [1, 2]. Myotonic dystrophy type 1 (DM1) is inherited in an autosomal dominant pattern, and it is associated with trinucleotide CTG repeats expansion in the 3′ non-coding region of the *DMPK* (myotonic dystrophy protein kinase) gene. Main clinical manifestations of DM1 are progressive, primarily distal muscular weakness and atrophy, myotonia, cataract, central nervous system affection, and cardiac involvement [3]. On the other hand, myotonic dystrophy type 2 is caused by the mutation in the intron of *CNBP* (CCHC-type zinc finger nucleic acid binding protein) gene [4]. DM2 is predominantly characterized by proximal muscle weakness, myotonia, cataract, and the involvement of the brain, heart and other organ systems [2, 5]. In contrast to DM1, DM2 patients have a milder clinical presentation, later disease onset, and better prognosis [1, 2, 6].

Patients with different neuromuscular disorders often have an increased percentage of body fat tissue together with a decrease in a total muscle mass [7]. The accumulation of adipose tissue may additionally complicate patients' mobility and compromise their respiration. People with DM1 have increased body mass index (BMI), longer waist circumference,

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and a higher percentage of body fat in contrast to healthy people (matched for gender and age) [8, 9]. Furthermore, DM1 patients had increased percentage of fat mass in trunk, arms, and legs, even if they have normal BMI [10, 11]. Compared to DM1, patients with DM2 seem to have obesity and metabolic disorders more frequently although they have milder muscle weakness. However, there are no many studies focusing on this topic and in one of them BMI was similar in DM1 and DM2 [12]. Further research is needed to determine similarities and differences of body composition in patients with DM1 and DM2.

The aim of this study was to analyze body composition, as well as its association with sociodemographic and clinical characteristics of DM1 and DM2 patients.

Methods

Twenty DM1 and 12 DM2 patients were recruited consecutively from the Inpatient Unit and the Day Hospital of the Neurology Clinic, from January 1, 2016 to June 30, 2017. The clinical and electrophysiological diagnosis of DM1 and DM2 was confirmed by genetic analysis using a repeat primed-PCR [13]. Patients with comorbid disorders, which are not part of the multisystemic presentation of DM, were excluded. We also excluded patients with congenital or late adult forms of DM1, as they have been shown to have different phenotypes. Approval was received from the Ethics Committee of the School of Medicine, University of Belgrade. Informed consent was obtained from all individual participants included in the study.

Data including gender, age, age at the onset of the disease, and the disease duration were collected for all patients. Due to the fact that the Muscular Impairment Rating Scale (MIRS) [14] could not be applied in DM2 patients, muscle strength of DM2 and DM1 patients was documented according to the Medical Research Council 0–5 point scale (0 = no movement, 5 = normal strength) based on manual muscle testing [15]. Following muscles were examined bilaterally: shoulder abductors and adductors, elbow flexors and extensors, wrist flexors and extensors, long finger flexors and extensors, thumb opponents, finger abductors and adductors, hip flexors, extensors, abductors and adductors, knee flexors and extensors, and ankle plantar and dorsal flexors. Overall severity of motor impairment was analyzed by adding strength of the weakest muscle of the proximal/distal muscle groups of the arms/legs in all patients with maximum score being 20 and lower score meaning greater muscle impairment [16].

We also assessed multi-systemic affection of DM patients including systolic and diastolic blood pressure, electrocardiography (ECG) and echocardiography abnormalities, forced vital capacity (FVC), and laboratory analysis (glycemia, oral glucose tolerance test (OGTT), serum insulin, triglycerides, cholesterol, HDL, and LDL cholesterol). In some patients, levels of 25(OH) vitamin D and parathyroid hormone (PTH) were also analyzed in sera. Severe ECG abnormalities were defined as reported by Groh et al. [17]. Concomitant medications were also noted.

Body mass index (BMI) was calculated as a body mass (in kilograms) divided by squared height (in meters). Body composition analysis was performed using the DEXA (dual energy x-ray absorptiometry) on the Hologic machine (Marlborough, Massachusetts, USA). DEXA is a non-invasive technique for body composition analysis which allows regional assessment of the proportion of fat and non-fat tissue [9]. It is used in the analysis of a complete or a regional body composition. By using the software, body was divided into six parts (head, trunk, left and right arm, left and right leg). In order to assess body composition, the model of three sections was applied: bone mineral content (BMC), fat mass (FM), and lean tissue mass (LTM). LTMI (lean tissue mass index = lean tissue mass/squared height), FMI (fat mass index = fat mass/squared height), the trunk/limb fat index (TLFI = trunk fat mass/limb fat mass) and BMD (bone mineral density) were also calculated.

Statistical data processing was performed in the SPSS version 20.0. All examined variables were analyzed using the Kolmogorov-Smirnov test in order to determine if they were distributed by normal distribution. The proportion, mean, and standard deviation (SD) were used as descriptive statistics parameters. Significance of statistical difference between two groups was investigated using Mann-Whitney U test or Student's t test. Correlations were analyzed using Sperman's correlation coefficient. Level of significance in all statistical analyses was 0.05 for statistically significant differences and 0.01 for high statistically significant differences.

Results

DM1 and DM2 groups did not differ statistically regarding gender, age, and disease duration (Table 1). Patients with DM2 had a milder muscle weakness, better pulmonary functions, and higher diastolic blood pressure. There were no significant differences in laboratory findings among groups (Table 2).

The analysis of the overall body composition is shown in Table 3. Although DM1 and DM2 patients had a similar total body mass, BMC, FM, and LTM, it was observed that DM1 patients had higher TLFI which indicates increased fat accumulation in the trunk (i.e., visceral obesity). The analysis of the body composition of individual body regions is shown in Table 4. There were no significant differences between two groups of patients. The bone density analysis of the individual parts of the body showed that patients with DM2 had more reduced bone density in almost all regions although statistical

Table 1 Main socio-demographic and clinical characteristics of patients with DM1 and DM2

Features	DM1	DM2
N	20	12
Male gender (%)	50.0	16.7
Age (years, mean ± SD)	41.8 ± 12.2	49.9 ± 13.1
Disease duration (years, mean ± SD)	15.1 ± 9.4	15.9 ± 12.1
MRC sum score (mean ± SD)*	17.8 ± 2.2	19.8 ± 2.3
Arms proximal	4.6 ± 0.6	4.4 ± 1.4
Arms distal**	3.6 ± 0.7	4.5 ± 0.5
Legs proximal**	4.8 ± 0.4	4.0 ± 0.6
Legs distal**	3.6 ± 0.8	4.6 ± 0.5
FVC (%, mean ± SD)**	86.9 ± 14.9	121.7 ± 15.2
FVC under 90% (%)**	64.7	0.0
Severe ECG (%)	33.3	18.2
EF (%, mean ± SD)	62.7 ± 3.1	61.4 ± 5.6
EF under 55 (%)	0.0	12.5
Systolic blood pressure (mmHg, mean ± SD)	113.9 ± 15.4	123.3 ± 13.7
Diastolic blood pressure (mmHg, mean ± SD)*	73.1 ± 10.5	81.7 ± 9.6
Arterial hypertension (%)	22.2	33.3
BMI (kg/m^2) (mean ± SD)	26.8 ± 9.1	25.1 ± 4.6
BMI > 25 kg/m^2 (%)	50.0	58.3

DM1, myotonic dystrophy type 1; *DM2*, myotonic dystrophy type 2; *N*, number of patients; *SD*, standard deviation; *MRC*, Medical Research Council; *FVC*, forced vital capacity; *EF*, ejection fraction; *BMI*, body mass index; *$p < 0.05$; **$p < 0.01$

significance was reached only for the right ribs compared to DM1 patients (Table 5).

We correlated DEXA parameters with sociodemographic and clinical findings in all DM1 and DM2 patients. In DM1 group, higher LTMI (16.7 ± 3.3 vs. 13.6 ± 2.3, $p < 0.05$) and BMD were observed in men compared to women (1.23 ± 0.11 to 1, 12 ± 0.07, $p < 0.05$). FMI correlated with age ($\rho = +0.58$, $p < 0.01$), BMI ($\rho = +0.67$, $p < 0.01$), total cholesterol and LDL cholesterol ($\rho = +0.74$ and $\rho = +0.56$, $p < 0.01$, respectively). The percentage of FM in legs was in reverse correlation with the muscle strength of the upper legs ($\rho = -0.47$, $p < 0.05$).

BMD correlated with age in patients with DM2 ($\rho = -0.68$, $p < 0.05$). FMI correlated with BMI and serum insulin level ($\rho = +0.73$ and $\rho = +0.74$, $p < 0.01$). The MRC sum score was associated with FMI ($\rho = -0.65$, $p < 0.05$) and BMD ($\rho = +0.72$, $p < 0.05$). Strength of individual muscle groups correlated with BMD in DM2 patients ($\rho = +0.62$, $p < 0.05$ for upper arm muscles, $\rho = +0.87$, $p < 0.01$ for forearm muscles, $\rho = +0.72$, $p < 0.05$ for lower leg muscles).

Discussion

Obesity was present in 50% of our DM1 and 58% of DM2 patients according to BMI. Analysis of the body composition showed that higher trunk-limb fat index (TLFI) is higher in DM1, which is supportive of visceral obesity. Similar results were published by Sedehizadeh et al. who found an increased fat index in the trunk area in patients with DM1 compared to anthropometrically matched healthy controls [18]. Previous studies showed that increased TLFI has been reported even in DM1 patients who did not have increased BMI [11]. In patients with muscular dystrophies, an increase in fat mass is associated with fatty infiltration into atrophic muscle tissue and not only in adipose tissue [11]. These results indicate that BMI is not a precise indicator of visceral obesity in these patients. However, moderate correlation between BMI and fat mass index (FMI) was observed in our patients.

We found correlation of FMI with higher serum LDL cholesterol in DM1 group and with insulinemia in DM2 group. Renna and colleagues recently indicated that besides alteration of insulin receptor splicing, post-receptor signaling abnormalities might contribute to insulin resistance in both DM1 and DM2 [19]. Visceral obesity, insulin resistance, and dyslipidemia are the main components of the metabolic syndrome, which is a major risk factor for cardiovascular diseases and diabetes mellitus type 2. Previous studies found correlation between visceral obesity and hypogonadism and testosterone levels in patients with DM1 [20]. It seems that visceral obesity and metabolic impairments may significantly contribute to the multisystemic manifestations of DM.

In a previous study, significant correlation was found between percentage of the body fat and the degree of muscle

Table 2 Laboratory findings in patients with DM1 and DM2

Features	DM1	DM2
N	20	12
Glycemia (mmol/L, mean ± SD)	6.3 ± 3.8	5.0 ± 0.9
Insulin (IU/mL, mean ± SD)	10.3 ± 5.9	27.1 ± 25.6
HOMA index (mean ± SD)	2.3 ± 1.6	2.7 ± 1.8
OGTT 120 min (mmol/L, mean ± SD)	7.4 ± 2.9	5.6 ± 0.5
Glucose metabolism (%)		
Normal	61.1	58.3
Insulin resistance	16.7	25.0
Glucose intolerance	5.6	0.0
Diabetes mellitus	16.7	16.7
Triglycerides (mmol/L, mean ± SD)	1.7 ± 0.7	1.8 ± 0.7
Triglycerides > 1.7 mmol/L (%)	44.4	45.5
Cholesterol (mmol/L, mean ± SD)	5.2 ± 1.2	5.9 ± 1.2
Cholesterol > 5.2 mmol/L (%)	61.1	72.7
HDL cholesterol (mmol/L, mean ± SD)	1.6 ± 0.6	1.9 ± 0.6
HDL cholesterol < 1.0 mmol/L (%)	12.5	0
LDL cholesterol (mmol/L, mean ± SD)	2.9 ± 1.2	3.5 ± 1.2
LDL cholesterol > 3.4 mmol/L (%)	38.9	50
25(OH) vitamin D (nmol/L, mean ± SD)[a]	43.8 ± 20.7	44.8 ± 25.5
25(OH) vitamin D < 75 nmol/L[a]	100.0	80.0
PTH (ng/L, mean ± SD)[b]		
PTH < 15 ng/L (%)[b]	12.5	0.0
15–68 ng/L (%)	75.0	100.0
> 68 ng/L (%)	12.5	0.0

DM1, myotonic dystrophy type 1; DM2, myotonic dystrophy type 2; *N*, number of patients; *SD*, standard deviation; *HOMA*, homeostasis model assessment; *OGTT*, oral glucose tolerance test; *HDL*, high density lipoprotein; *LDL*, low density lipoprotein; *PTH*, parathyroid hormone; [a] Level of 25(OH) vitamin D was available only for 8 DM1 and 5 DM2 patients; [b] Level of PTH was available only for 8 DM1 and 3 DM2 patients

weakness in DM1 [9]. Another study showed that the overall score on the MDHI questionnaire (patient-reported outcome measure) was in correlation with the percentage of total muscle mass in patients with DM1 [21]. In accordance with these findings, we observed that the percentage of adipose tissue in legs correlated with the weakness of upper leg muscles in DM1. Similarly, MRC sum score correlated with FMI in DM2 patients. Thus, amount of the fat mass in certain parts of the body might be a potential biomarker of response on gene therapy in future clinical trials, but further studies are needed to confirm this speculation. Recent publication showed that a cross talk between adipose tissue, muscles, and bones may be mediated by irisin; thus, this hormone may be a serum biomarker of muscle and bone mass reduction in DM [22]. It is also thought that obesity may contribute to lung restriction in DM1 [23], but this was not confirmed in our study.

Bone density in the right ribs was lower in DM2 group compared to DM1. The main risk factors for osteoporosis in a general population are age, female gender, postmenopausal period in women, smoking, alcohol, hypogonadism, and chronic use of corticosteroids and others. Besides these general risk factors, there are some DM-specific such as androgenic failure, malabsorption, decreased muscular activity, and less exposure to sun. [24]. Two recent researches showed that vitamin D deficiency was common among DM1 and DM2 patients [25, 26]. Similar was observed in our cohort. Even more, increased adiposity in DM may be a risk factor for hypovitaminosis D [26]. As a consequence of vitamin D deficiency, secondary hyperparathyroidism can occur [25] which results in the degradation of the bones. Since muscle weakness (particularly proximal) is known to be a complication of hyperparathyroidism, this can also contribute to the DM phenotype. This confirms once again that all components of adipose tissue—muscle tissue—bone axis are intercorrelated in many different ways. In accordance with the literature data, we observed significant correlation between BDM and muscle strength in DM2 patients. Significant correlations between muscle mass, strength, and disease severity on one side and parathyroid hormone (PTH) serum levels on the other side were observed in patients with DM1 [25]. It seems that the use of oral supplements of vitamin D could modulate muscle weakness [26].

Table 3 Analysis of the overall body composition using DEXA in patients with DM1 and DM2

DEXA features	DM1	DM2
N	20	12
Total body mass (g) (mean ± SD)	69,457.7 ± 17,539.4	69,038.3 ± 16,004.3
BMC (g) (mean ± SD)	2396.5 ± 474.1	2263.1 ± 603.2
FM (g) (mean ± SD)	23,196.8 ± 8054.0	23,777.7 ± 8750.3
LTM (g) (mean ± SD)	42,997.2 ± 11,586.3	42,997.2 ± 10,736.9
% of fat tissue (mean ± SD)	32.9 ± 7.2	33.8 ± 10.0
FMI (kg/m^2) (mean ± SD)	8.1 ± 2.9	8.6 ± 3.3
LTMI (kg/m^2) (mean ± SD)	15.2 ± 3.2	15.3 ± 2.8
TLFI (mean ± SD)*	1.16 ± 0.32	0.87 ± 0.23
BMD (g/cm^3) (mean ± SD)	1.2 ± 0.1	1.1 ± 0.2

DEXA, dual-energy x-ray absorptiometry; *DM1*, myotonic dystrophy type 1; *DM2*, myotonic dystrophy type 2; *N*, number of patients; *SD*, standard deviation; *BMC*, bone mineral content; *FM*, fat mass; *LTM*, lean tissue mass; *FMI*, fat mass index; *LMI*, lean time mass index; *TLFI*, trunk limb fat index; *BMD*, bone mineral density; *$p < 0.05$

Table 4 Regional body composition analysis with DEXA in patients with DM1 and DM2

DEXA features	DM1	DM2
N	20	12
Left arm		
FM (g) (mean ± SD)	1564.3 ± 748.8	1697.6 ± 649.8
LTM (meant ± SD)	2253.3 ± 930.4	2267.5 ± 803.7
Right arm		
FM (g) (mean ± SD)	1541.1 ± 645.4	1723.7 ± 703.5
LTM (g) (mean ± SD)	2348.1 ± 910.9	2277.8 ± 647.2
Trunk		
FM (g) (mean ± SD)	12,019.1 ± 5262.8	10,792.1 ± 4928.5
LTM (g) (mean ± SD)	22,983.9 ± 6352.9	22,339.2 ± 4444.8
Left leg		
FM (g) (mean ± SD)	3495.5 ± 952	4271.5 ± 1450.3
LTM (g) (mean ± SD)	6106.0 ± 1553.2	55,272.0 ± 170,117.0
Right leg		
FM (g) (mean ± SD)	3559.6 ± 1011.7	4339.1 ± 1469.6
LTM (g) (mean ± SD)	6416.9 ± 1692	6404.8 ± 2508.5

DEXA, dual-energy x-ray absorptiometry; *DM1*, myotonic dystrophy type 1; *DM2*, myotonic dystrophy type 2; *FM*, fat mass; *LTM*, lean tissue mass; *N*, number of patients; *SD*, standard deviation

There are several limitations of this study. First, sample size is small. Second, there were no healthy control group but it is particularly complicated to find relevant age-, gender,- and antropometrically matched controls. Third, although there were no statistical differences between DM1 and DM2 subjects regarding gender, age, and disease duration, female subject predominance was obvious in DM2 group. Previous data showed that gender may affect phenotype in DM1 and DM2 [27, 28]. There is a lack of relevant epidemiological data about DM2, but in the majority of studies, the number of women is higher than men; thus, our DM2 cohort is representative. Difference in age between patients with DM1 and DM2 can be explained by the later onset of DM2, which most commonly occurs in the fourth decade [2, 29]. Another limitation is lack of data on vitamin D and PTH serum levels in majority of tested patients.

Table 5 Bone mineral density in patients with DM1 and DM2

DEXA features	DM1	DM2
N	20	12
BMD (g/cm^3) (mean ± SD)	1.18 ± 0.11	1.12 ± 0.15
Head BMD (g/cm^3) (mean ± SD)	2.47 ± 0.35	2.35 ± 0.36
Left arm BMD (g/cm^3) (mean ± SD)	0.75 ± 0.09	0.71 ± 0.09
Right arm BMD (g/cm^3) (mean ± SD)	0.75 ± 0.08	0.73 ± 0.1
Left ribs BMD (g/cm^3) (mean ± SD)	0.66 ± 0.07	0.62 ± 0.11
Right ribs BMD (g/cm^3) (mean ± SD)*	0.68 ± 0.07	0.61 ± 0.09
Thoracic spine BMD (g/cm^3) (mean ± SD)	0.98 ± 0.16	1.01 ± 0.25
Lumbar spine BMD (g/cm^3) (mean ± SD)	1.17 ± 0.17	1.13 ± 0.24
Pelvis BMD (g/cm^3) (mean ± SD)	1.20 ± 0.13	1.12 ± 0.25
Left leg BMD (g/cm^3) (mean ± SD)	1.14 ± 0.14	1.08 ± 0.18
Right leg BMD (g/cm^3) (mean ± SD)	1.14 ± 0.13	1.1 ± 0.18

DEXA, dual-energy x-ray absorptiometry; *DM1*, myotonic dystrophy type 1; *DM2*, myotonic dystrophy type 2; *N*, number of patients; *SD*, standard deviation; *BMD*, bone mineral density; *$p < 0.05$

Conclusion

Visceral fat deposition is more common in patients with DM1, and the percentage of fat mass was in correlation with the degree of muscular weakness in upper legs. Also, FMI correlated with overall muscle strength in DM2. Decreased bone mineral density was observed in patients with DM2 and it correlated with the degree of muscle weakness. Prophylactic and therapeutic measures for the correction of obesity and osteoporosis should be applied in DM. Since some DEXA parameters correlated with muscle strength, these measures might be used as objective biomarkers of gene therapy effects in future clinical trials. However, prospective studies in larger cohorts are needed to confirm this speculation.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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