Metabolic impairments in patients with myotonic dystrophy type 2

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Objectives: metabolic syndrome (MetS) increases risk of cardiovascular diseases and diabetes mellitus type 2. Aim of this study was to investigate frequency and features of MetS in a large cohort of patients with DM2.

Materials & methods: this cross-sectional study included 47 DM2 patients. Patients were matched with 94 healthy controls (HCs) for gender and age. MetS was diagnosed according to the new worldwide consensus criteria from 2009.

Results: mean age of DM2 patients was 52 ± 11 years, 15 (32%) were males, and mean disease duration was 15 ± 14 years. MetS was present in 53% of DM2 patients and 46% of HCs (p > 0.05). All components of the MetS appeared with the similar frequency in DM2 and HCs, respectively: hypertension 64 vs 52%, central obesity 62 vs 74%, hypertriglyceridemia 49 vs 39%, hyperglycemia 49 vs 39%, low HDL cholesterol 42 vs 39%, and hyperinsulinemia 42 vs 39% (p > 0.05). DM2 patients were more commonly on lipid lowering therapy compared to HCs (12 vs 3%, p = 0.05). Fifteen (32%) patients with DM2 and only one (1%) subject from control group had diabetes mellitus (p < 0.01). Insulin resistance was found in thirty (65%) patients with DM2. Presence of MetS was not associated with patient’s gender, age, severity nor duration of the disease (p > 0.05).

Conclusions: more than half of DM2 subjects met the criteria for the MetS. We suppose that treatment of metabolic disturbances may reduce cardiovascular complications and improve quality of life in patients with DM2, which is progressive and still incurable disorder.

Key words: myotonic dystrophy type 2, metabolic syndrome, obesity

Introduction

Myotonic dystrophy type 2 (DM2) is an autosomal dominant, slowly progressive, multi-systemic disease, caused by CCTG repeat expansion in intron 1 of the CNBP gene that codes protein called CCHC-type zinc finger nucleic acid binding protein (1). Metabolic syndrome (MetS) is a cluster of metabolic and hemodynamic disturbances that appear together, and multiply risk of cardiovascular diseases and diabetes mellitus type 2 (2).

Patients with neuromuscular diseases (NMD) have a higher frequency of cardiovascular and metabolic impairments in comparison to general population, which is probably caused by muscle weakness, fatigue and reduced mobility (3, 4). MetS was found in 55% of 11 patients with different slowly progressive NMD, and all components of MetS were more frequent in NMD patients in comparison to healthy controls (HCs) (3). Also, total energy expenditure was significantly lower in patient group.

We have previously reported a high frequency of metabolic disorders in myotonic dystrophy type 1 (DM1), but only 17% of these patients fulfilled criteria for the diagnosis of MetS (5). Nevertheless, in the study by Shieh et al. different MetS criteria were applied and frequency of MetS in DM1 was 41% (6).

There are no studies that specifically examined frequency of MetS in DM2 patients. It seems that DM2 patients have more severe metabolic impairments compared to DM1 (1,7). Some authors suggested that diabetes mellitus type 2 and arterial hypertension are more frequent in DM2 than in DM1 (8, 9). Also, hypertriglyceridemia and hypercholesterolemia are probably more common in DM2 than in DM1 (7). There are even some suggestions that DM2 patients, unlike DM1 patients, may frequently have atherosclerosis and coronary heart disease (1).
Aim of this study was to investigate frequency and features of the MetS in a large cohort of patients with DM2.

Methods

Forty seven DM2 patients (mean age 51.9 ± 11.1 years, 31.9% males) were recruited consecutively from the Outpatient and Inpatient Units of the Neurology Clinic, Clinical Centre of Serbia, University of Belgrade, from January 1, 2015 to December 31, 2015. All patients had multi-systemic features of DM2 and no other comorbidities. DM2 patients were matched for gender and age with 94 HCs (mean age 51.9 ± 11.1 years, 31.9% males). Control group comprised of patients’ healthy family members and staff of the Neurology Clinic, Clinical Centre of Serbia, University of Belgrade. Study was approved by the Ethics Committee of the School of Medicine, University of Belgrade, and written informed consent was obtained from all subjects participating in the study.

Clinical and electrophysiological diagnosis of DM2 was confirmed by standard PCR and repeat primed-PCR assessing the presence of increased CCTG repeats in the CNBP gene (10). Severity of muscle weakness was assessed by the Medical Research Council scale, ranging from 0 to 5 (0 = no muscle contraction, 5 = normal muscle strength) (11). Manual muscle testing of all patients was performed by two neurologists (V.R.S. and S.P.). Following muscles were tested bilaterally: shoulder abductors and adductors, elbow flexors and extensors, wrist flexors and extensors, finger flexors and extensors, thumb opponens, hip flexors, extensors, abductors and adductors, knee flexors and extensors, ankle plantar and dorsal flexors. We added strength of the weakest muscle of the proximal and distal muscle groups of upper and lower limbs with maximum score being 20 (12).

MetS was defined according to the joint statement of the International Diabetes Federation Task Force on Epidemiology and Prevention, the National Heart, Lung, and Blood Institute, the American Heart Association, the World Heart Organization (WHO), the International Atherosclerosis Society, and the International Association for the Study of Obesity (13). MetS was diagnosed when at least three of five criteria were present:

1. increased waist circumference (≥ 94 cm for men and ≥ 80 cm for women);
2. increased serum triglyceride level (≥ 1.7 mmol/L) or use of lipid lowering agents;
3. reduced serum level of high-density lipoprotein (HDL) cholesterol (< 1.0 mmol/L for men and < 1.3 mmol/L for women);
4. elevated blood pressure (≥ systolic 130 mmHg and/or diastolic ≥ 85 mmHg), diagnosis of hypertension, or use of antihypertensive drugs;
5. increased serum fasting glucose level (≥ 5.6 mmol/L) or use of antidiabetic drugs.

Fasting serum levels of total, HDL and LDL cholesterol, as well as of triglycerides and glucose, were measured by standard laboratory methods. Fasting plasma insulin concentration was measured using radioimmunoassay (RIA), and normal values according to our laboratory are 5-25 mIU/L. HOMA (Homeostasis Model Assessment) index of insulin resistance (IR) was calculated according to the following formula: glycemia (mmol/L) x insulin (mU/L)/22.5 (14). IR was defined if HOMA index was higher than 2.6 (15).

Body mass index (BMI) was calculated as weight divided by squared height (kg/m²). Nutritional status was assessed using the WHO guidelines: underweighted if BMI < 18.5 kg/m², well nourished if BMI 18.5-25.0 kg/m², overweighted if BMI 25-30 kg/m², and obese if BMI > 30 kg/m² (16).

Normality of data was tested by the Kolmogorov-Smirnov test. For comparison between two groups (DM2 patients vs HCs and DM2 patients with certain metabolic impairment vs DM2 patients without certain metabolic impairment), chi-square test, Mann-Whitney U-test, and Student t-test were used. In all statistical analyses, significant testing was two-sided, with p level set up at 0.05 (statistically significant) and 0.01 (highly statistically significant).

Results

A total number of 47 DM2 patients were included (Table 1). MetS was present in 25 (53.2%) DM2 patients and 43 (45.7%) HCs (p > 0.05). Mean number of MetS components was similar in both groups (2.4 ± 1.4 vs 2.4 ± 1.3; p > 0.05). Frequency of the individual components of MetS is shown in Figure 1, while metabolic and

| Sociodemographic and clinical data | DM2 patients |
|-----------------------------------|-------------|
| Gender (% males)                  | 31.9        |
| Age (x ± SD, years)               | 51.9 ± 11.1 |
| Education (x ± SD, years)         | 11.3 ± 3.1  |
| Age at onset (x ± SD, years)      | 37.2 ± 11.1 |
| Disease duration (x ± SD, years)  | 15.0 ± 13.7 |
| Muscle weakness (MRC)             |             |
| upper limb - proximal             | 4.3 ± 0.6   |
| upper limb - distal               | 4.4 ± 0.7   |
| lower limb - proximal             | 3.9 ± 0.7   |
| lower limb - distal               | 4.5 ± 0.7   |
| total                             | 17.0 ± 2.1  |

x: mean value; SD: standard deviation; MRC: Medical Research Council.
hemodynamic parameters are presented in Table 2. Arterial hypertension was present in 63.8% of DM2 patients and 52.1% of HCs \((p > 0.05)\). Visceral obesity was present in 61.7% of DM2 patients and 74.5% of HCs \((p > 0.05)\). Mean BMI in DM2 patients was \(25.2 \pm 3.6 \text{ kg/m}^2\): 15% were undernourished, 51% of them were well-nourished, 27% were overweighted, and 7% obese.

Hypertriglyceridemia was present in 48.9% of patients with DM2 and 38.7% of HCs \((p > 0.05)\). Low HDL cholesterol level was found in 29.8% of DM2 patients and 41.5% of HCs \((p > 0.05)\). However, DM2 patients were more frequently on lipid lowering therapy (11.6% vs 3.2%, \(p = 0.05\)).

Majority of DM2 patients had IR (63.8%). Diabetes mellitus type 2 was present in 31.9% and glucose intolerance in 3.4% of patients. Patients with DM2 were more likely to be on oral hypoglycemic medications and/or insulin therapy than HCs (27.6% vs 1.1%, \(p < 0.01\)).

There were no significant differences in the frequency of MetS, hypertension, dyslipidaemia and hyperglycaemia between men and women with DM2 \((p > 0.05)\). On the other hand, central obesity was more common in women than in men 75.0% vs 33.3% \((p < 0.01)\). DM2 patients with hypertension were more likely to be older than normotensive ones \((55.7 \pm 9.0 \text{ years} \text{ vs } 45.2 \pm 11.5 \text{ years}, p < 0.01)\). Frequency of MetS and its components showed

**Table 2.** Metabolic and hemodynamic parameters in DM2 patients and HCs.

| Parameter                        | DM2 patients \((n = 47)\) | HCs \((n = 94)\) |
|----------------------------------|---------------------------|-----------------|
| Waist circumference \((x \pm SD, \text{ cm})\) | \(91.4 \pm 11.1\)         | \(92.6 \pm 12.5\) |
| Systolic blood pressure \((x \pm SD, \text{ mmHg})\) | \(128.6 \pm 16.6\)        | \(125.4 \pm 16.7\) |
| Diastolic blood pressure \((x \pm SD, \text{ mmHg})^*\) | \(82.2 \pm 8.8\)          | \(78.8 \pm 10.1\) |
| Glycemia \((x \pm SD, \text{ mmol/l})\) | \(5.9 \pm 3.0\)           | \(5.4 \pm 0.7\)  |
| Triglycerides \((x \pm SD, \text{ mmol/l})\) | \(1.8 \pm 0.9\)           | \(1.6 \pm 1.5\)  |
| Total cholesterol \((x \pm SD, \text{ mmol/l})^{**}\) | \(6.2 \pm 1.5\)           | \(5.3 \pm 1.1\)  |
| HDL \((x \pm SD, \text{ mmol/l})^{**}\) | \(1.6 \pm 0.5\)           | \(1.3 \pm 0.6\)  |
| LDL \((x \pm SD, \text{ mmol/l})^{**}\) | \(3.9 \pm 1.3\)           | \(3.0 \pm 0.9\)  |

\(x:\) mean value; \(SD:\) standard deviation; HDL: high-density lipoprotein, LDL: low-density lipoprotein; \(^* p < 0.05,^{**} p < 0.01\).
no correlation with patients’ age (p > 0.05). In addition, there was no correlation of muscle strength, disease duration and level of education with the frequency of MetS and its components (p > 0.05).

**Discussion**

Half of our DM2 patients had MetS. In patients with DM1 MetS prevalence ranged from 17% to 41% depending on the criteria (5, 6). Higher frequency of MetS in patients with DM2 compared to DM1 may be due to the later onset and later diagnosis of DM2 (9, 12, 17). Similarly, frequency of the MetS in a general population depends on the age of population studied (18). Azizi et al found that frequency of MetS increased from < 5.6% in participants aged 30-39 years to 17.5% in participants aged 60-69 years (19). MetS was present in 42% of subjects older than 70 (20). MetS was also common (45.7%) in our HCs with mean age of 51 years. This is in accordance with the findings of Djokic et al. who found MetS in 28% of patients aged 40-49 and 43% of patients aged 50-59 at the primary health care institutions in Serbia (21).

Majority of studies found that arterial hypertension is the most frequent component of the MetS in general population (22). Similarly, arterial hypertension was the most common component of the MetS (64%) in our DM2 cohort. Furthermore, DM2 patients had a higher mean diastolic pressure compared to the control group (82.2 ± 8.8 mmHg vs 78.8 ± 10.1 mmHg, p < 0.05). On the other hand, arterial hypertension was present in only 18% of DM1 patients, and even arterial hypotension is common in this disease (5). Difference in the prevalence of arterial hypertension in DM1 versus DM2 patients may be due to the different molecular genetic mechanisms of these two conditions (23).

Visceral obesity was the second most common component of the MetS in our cohort (61.7%). Literature data on visceral obesity in DM2 patients are very limited. Visceral obesity and IR are considered to be the key components of the MetS (2). In our cohort, 34% of DM2 patients were overweight or obese. Tieleman et al. found that mean BMI was similar in patients with DM2 and DM1 (24). On the other hand, DM1 patients were found to have a higher BMI, longer waist circumference and higher percentage of fat compared to age matched controls (4, 25). Although obesity can occur as a consequence of the physical inactivity due to the muscle weakness, Gagnon et al. found obese DM1 patients even among those with mild muscle weakness (26). This suggest the importance of investigating other risk factors for obesity, such as socio-economic status, and lifestyle habits including eating high-calorie food rich in fat and carbohydrates (26).

Serum triglycerides were elevated in approximately 50% of our DM2 patients, and mean serum total cholesterol and LDL cholesterol were significantly higher in DM2 than in HCs. It is of note that levels of good cholesterol, i.e. HDL, were also higher in DM2. In a small cohort of 20 DM2 patients, Heatwole et al. reported hypercholesterolemia in 63% and hypertriglyceridemia in 26% percent of DM2 patients (7). In our previous study dyslipidaemia was the most common component of the MetS in patients with DM1 - 67% of patients had elevated triglycerides, while 35% had low HDL level (5). Around 12% of DM2 patients were on cholesterol lowering therapy which is of a practical importance because statins may worsen muscle weakness. It is well known that DM2 can be diagnosed in some patients with myalgias after introduction of the cholesterol lowering therapy (27).

IR was diagnosed in 64% and diabetes mellitus type 2 in 32% of our DM2 patients. Savkur et al. demonstrated that aberrant regulation of the alternative splicing of insulin receptor is associated with insulin resistance in DM (28). Impaired insulin secretion, reduction of lean body mass and increased serum leptin levels are other mechanisms associated with IR (25, 29). Renna and colleagues recently reported that DM skeletal muscle exhibits alterations of post-receptor signalling (including basal phosphorylation levels of Akt/PKB, p70S6K, GSK3β and ERK1/2), regardless of the alteration of insulin receptor splicing (30). Frequency of diabetes in our DM2 patients was higher than previously reported frequency in DM1. This suggests that eventual mechanisms that protect DM1 patients from development of diabetes, may not be present in DM2.

Although prevalence of MetS increases with age in a general population, in our DM2 cohort this correlation was not observed. On the other hand, we found association between arterial hypertension and aging which is similar to the findings from a general population (31). Disease duration and muscle weakness showed no correlation with MetS. This suggests that muscle weakness is not the key factor for development of MetS in DM2.

The main limitations of our study are lack of data regarding insulin levels and HOMA index in HC group, and lack of data on testosterone level in DM2 subjects since testosterone may have influence on visceral obesity and insulin resistance in DM1 and DM2 (32, 33). On the other hand, it is of note that none of our patients received testosterone therapy.

**Conclusions**

MetS was common in DM2 patients but not more frequent than in HCs. Regular screening for metabolic and hemodynamic disturbances in DM2 would enable early diagnosis and therapy. We suppose that treatment of metabolic disturbances may reduce cardiovascular complications and improve quality of life in patients with DM2, which is progressive and still incurable disorder.
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