

# Hypogonadism and erectile dysfunction in myotonic dystrophy type 1

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Myotonic dystrophy type 1 (DM1) is the most common form of muscular dystrophy in adults. It affects many organs and systems besides muscle. Aim of this study was to assess frequency of erectile dysfunction (ED) and hypogonadism, the correlation between them and the impact of ED on quality of life (QoL) in patients with DM1. A series of 25 men (aged from 22 to 58 years) with a diagnosis of DM1 was analyzed. Muscular Impairment Rating Scale (MIRS) was used to assess severity of muscular involvement. Erectile function was assessed using the short form of the International Index of Erectile Function test (IIEF-5). Levels of follicle stimulating hormone (FSH), luteinizing hormone (LH) and testosterone were assessed. All patients completed the Serbian version of the SF-36 questionnaire as a measure of health-related QoL. ED was present in 18 (72%) of patients. Seven (28%) patients were euogonadic, 16 (64%) had compensated hypogonadism and 2 (8%) had primary hypogonadism. ED was somewhat more common in patients with hypogonadism (78% vs. 57%). Mental composite score of SF-36 was lower in patients with ED ( $p < 0.05$ ). Our results showed that 72% of men with DM1 had ED and hypogonadism. Studies with larger number of subjects are needed to resolve cascade of events that lays behind ED in DM1. Development of therapeutic strategies may have positive impact on QoL. Substitutive therapy with androgens may be beneficial.

**Key words:** myotonic dystrophy type 1, erectile dysfunction, hypogonadism

Myotonic dystrophy type 1 is the most common form of muscular dystrophy in adults with estimated prevalence of 1 to 35 patients on 100 000 inhabitants (1). It is an autosomal dominant disorder caused by expansion of unstable trinucleotide CTG repeats in DMPK gene on the long arm of the chromosome 19 (2). This mutation is responsible for premature aging of many organs and systems in DM1 (2). Endocrine disorders are common in

DM1 (3). Hypogonadism is also described with affection of both interstitial and tubular gonadic function (4).

Erectile dysfunction (ED) is defined as a persistent or recurrent inability to achieve and maintain a penile erection adequate for satisfactory sexual activity (5). It is reported that ED can be found among DM1 patients (6, 7), but there are not enough data about frequency and causes of this disorder. Also, effects of ED on personal and social life, as well as on quality of life (QoL) in DM1 men is still unclear.

Aim of this study was to assess frequency of erectile dysfunction (ED) and hypogonadism, the correlation between them and the impact of ED on health-related QoL in patients with DM1.

## Material and methods

The study included 25 men aged from 22 to 58 years which were consecutively recruited from the Inpatient and Outpatient Unit of Neurology Clinic, Clinical Center of Serbia, from October 1<sup>st</sup> 2011 until February 15<sup>th</sup> 2012. Genetic diagnosis of CTG repeat expansion was obtained for patients in addition to typical clinical and electromyographic data. Patients with congenital form of the disease, those with diabetes mellitus and with any other associated severe disease not related to DM1 were excluded from the study. Presence of depression was excluded by Hamilton depression scale applied by a trained physician. All patients gave informed consent to participate in the study and the study was approved by the Ethical Board of the Neurology Clinic.

Severity of muscular involvement was assessed using the Muscular Impairment Rating Scale (MIRS) (8). The MIRS is an ordinal five-point rating scale, established in

accordance with the clinically recognized distal to proximal progression of muscular involvement in DM1, and based partly on manual muscle testing of 11 muscle groups (8).

Erectile function was assessed using the International Index of Erectile Function test (IIEF) (9). IIEF is multi-dimensional instrument for the evaluation of male sexual function that has been adopted as the gold standard measure and has been recommended as a primary endpoint for clinical trials of ED, as well as for the diagnostic evaluation of its severity (10). For purposes of this study, we used shorter version of the questionnaire (IIEF-5), which was validated and rated as simple method for evaluation of ED (11). The possible scores for IIEF-5 range from 5 to 25. Degree of erectile dysfunction can be classified into five categories: severe (5-7), moderate (8-11), mild to moderate (12-16), mild (17-21) and no ED (22-25).

Levels of follicle stimulating hormone (FSH), luteinizing hormone (LH) and testosterone were assessed by electrochemiluminescence immunoassay. Normal values of our laboratory are 1.5-12.4 mIU/l for FSH, 1.7-8.6 mIU/l for LH and 8.64-29.0 nmol/l for testosterone. Regarding interstitial testicular function, patients with normal values of LH and testosterone were classified as eugonadic, those with increased LH and normal testosterone had compensated hypogonadism and those with increased LH and decreased testosterone had primary hypogonadism. Increased level of FSH indicated tubular failure of testicles.

All patients completed Serbian version of the SF-36 questionnaire as a measure of health-related QoL (12). The SF-36 is a generic instrument that measures eight general health concepts: physical functioning (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role emotional (RE) and mental health (MH). Two main scores are available to summarize these scales: physical composite score (PCS) and mental composite score (MCS), as well as total SF-36 score. All these scores fall within a 0-100 scale. Higher scores reflect better HRQoL.

Methods of descriptive statistic,  $\chi^2$  test for comparisons between nominal and ordinal variables and Mann-Whitney U test for comparisons between continuous non-parametric variables were used. In all analyses, significant testing was two-sided, with alpha set at 0.05 for statistical significance and 0.01 for high statistical significance.

## Results

Demographic and clinical characteristics of the patients are shown in Table 1.

Mean IIEF-5 score was  $16.4 \pm 6.2$ . Eighteen (72%) patients had ED. Mild ED was detected in 8 patients (32%), mild to moderate in 4 (16%), moderate in 3 (12%) and severe ED in 3 patient (12%).

**Table 1.** Demographic and clinical features of investigated men with DM1 (n = 25).

Age at onset (mean years $\pm$ SD)	25.9 $\pm$ 11.1
Duration of disease (mean years $\pm$ SD)	18.1 $\pm$ 10.1
Age (mean years $\pm$ SD)	44.0 $\pm$ 16.6
MIRS (%)	
II	20%
III	56%
IV	24%
CTG (mean number $\pm$ SD)	764.1 $\pm$ 281.1
CTG (%)	
E1	16%
E2	64%
E3	20%

MIRS – Muscular Impairment Rating Scale;

number of CTG repeats: E1 (100-500), E2 (500-1000), E3 (>1000)

Mean testosterone level in our DM1 patients was within normal range ( $16.8 \pm 6.5$  nmol/l), while mean LH and FSH levels were increased ( $11.5 \pm 4.4$  mIU/l and  $22.7 \pm 14.7$  mIU/l, respectively). Seven (28%) patients were eugonadic, 16 (64%) had compensated hypogonadism and 2 (8%) patients had primary hypogonadism. Increased FSH, index of tubular dysfunction, was registered in 15 (60%) patients and it was more frequent in DM1 men with androgenic dysfunction (88% vs. 20%,  $p < 0.01$ ).

Comparisons of different demographic and clinical features between patients with and without ED are presented in Table 2. Presence of ED was not in association with age at the onset of disease, age at the moment of investigation, duration of disease, number of CTG repeats and degree of muscle weakness. Difference in the hormones levels was not observed between patients with and without ED. Also, there was no significant association between tubular dysfunction of testicles and presence of ED. On the other hand, ED was more common in group of patients with interstitial dysfunction compared to eugonadic patients, though there was no statistical significance (78% vs. 57%).

Total SF-36 score in patients with ED was higher than in those without ED, but this difference did not reach the statistical significance. There was no statistical significance in these two groups regarding PCS, while MCS was significantly lower in patients with ED compared to those without ED ( $p = 0.040$ ) (Table 3).

## Discussion

Our study showed that 72% of males with DM1 had ED which was mild to moderate in average. In general population 5-20% of men have ED (13), while it is present in two thirds of DM1 males (6, 7), which is in accordance with our results.

**Table 2.** Comparison of demographic and clinical features between DM1 men with and without ED (n = 25).

Features	Men with ED (n=18)	Men without ED (n=7)	p value
Age at onset (mean years $\pm$ SD)	27.3 $\pm$ 12.4	22.4 $\pm$ 6.1	0.466
Duration of disease (mean years $\pm$ SD)	19.7 $\pm$ 10.7	13.9 $\pm$ 7.3	0.226
Age (mean years $\pm$ SD)	47.0 $\pm$ 18.4	36.3 $\pm$ 7.0	0.115
MIRS (%)			
II	22.2%	14.3%	
III	50.0%	71.4%	
IV	27.8%	14.3%	0.621
CTG (mean number $\pm$ SD)	782.8 $\pm$ 325.3	717.5 $\pm$ 127.4	0.533
FSH (mean mIU/l $\pm$ SD)	23.0 $\pm$ 14.5	21.5 $\pm$ 17.7	0.654
LH (mean mIU/l $\pm$ SD)	11.3 $\pm$ 4.2	12.7 $\pm$ 5.9	0.670
Testosterone (mean nmol/l $\pm$ SD)	16.0 $\pm$ 6.3	19.6 $\pm$ 7.2	0.347

ED – erectile dysfunction; MIRS – Muscular Impairment Rating Scale; FSH - follicle stimulating hormone, LH - luteinizing hormone; number of CTG repeats: E1 (100-500), E2 (500-1000), E3 (>1000)

**Table 3.** Comparison between DM1 men with and without ED (n=25)

Quality of life scores	Men with ED (n=18)	Men without ED (n=7)	p value
PCS	52.3 $\pm$ 21.7	69.9 $\pm$ 24.5	0.069
MCS	55.7 $\pm$ 22.2	75.9 $\pm$ 20.9	0.040
Total SF-36 score	55.3 $\pm$ 22.9	75.2 $\pm$ 23.4	0.053

ED – erectile dysfunction; PCS - physical composite score, MCS - mental composite score

Mean testosterone level in our DM1 patients was within normal range, while mean LH level was increased which is indicative of compensated hypogonadism. Primary and compensated hypogonadism are related to the damage of LH-testosterone axis. Almost half of DM1 patients according to Antonini et al shows some of these two forms of gonadal dysfunction (7), while Orngreen reported absolute androgen insufficiency in 38% of 97 DM1 patients (3).

Increased FSH level which indicates tubular dysfunction of testicles was detected in 60% of our patients and was more often in patients with androgenic disbalance. These results are in accordance with previous study on DM1 patients (7).

In our study, presence of ED was not in association with age at the onset of disease, age at the moment of investigation, duration of disease and degree of muscle weakness. On the other hand, frequency and severity of erectile dysfunction increase with age in general population (13). Some previous studies on DM1 males emphasized correlation between ED and number of CTG repeat, duration and severity of disease (7). Absence of this correlation in our study can be explained by relatively small number of patients. It is also possible that some other factors possibly related to DM1 may have significant impact on ED. Some of these factors are: impaired regulation of hemodynamics, dysfunction of smooth muscles of cavernous bodies, central impairment of nervous system control, psychological factors, dysfunction of the autonomic nervous system, numerous biochemical regulatory mechanisms etc. (14).

All these factors may not be in correlation with severity of muscular impairment and duration of disease.

ED was somewhat frequent in our patients with interstitial testicular failure in comparison with eugonadic patients, which is in accordance with previous results (7). It is known that ED is more frequent in patients with low testosterone level (15). Thus, parenteral administration of testosterone may be useful in the treatment of ED in DM1 (16). Besides the improvement of ED, testosterone may increase the rate of muscle protein synthesis, basal metabolic rate and body weight in DM1 men (17).

Different aspects of QoL in patients with DM1 were previously investigated (18, 19, 20), but to our best knowledge, this study is the first one that analyzed influence of ED on QoL. Our results showed impairment of QoL in DM1 patients, especially in the mental domains, which indicates negative psychological and social effect of ED. DM1 men usually have preserved sexual desire with inability to perform sexual act. Thus, the importance of development of therapeutic strategies for these patients may be of major significance. Since DM1 is still incurable disease, treatment of ED might improve QoL in these patients.

Main limitations of this study are its cross sectional design and small number of patients. Since only univariate analysis was performed, it is impossible to say if ED is an independent predictor of poorer QoL. Longitudinal studies with larger number of patients and multivariate regression analysis are needed.

## Conclusions

Our results showed that 72% of men with DM1 have ED, the same percentage (72%) have interstitial and 60% have tubular testicular failure. ED was more common in patients with interstitial impairment of testicles. Future studies with larger number of subjects should explain cascade of events that causes ED in men with DM1. Present findings may contribute to the development of adequate androgen substitution therapy to improve QoL in these patients.

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## References

- Kaufmann P. Progressive muscular dystrophies. In: Rowland L, ed. *Merritt's Neurology*. 11<sup>th</sup> ed. Philadelphia: LWW 2005.
- De Die-Smulders CE, Howeler CJ, Thijs C, et al. Age and causes of death in adult-onset myotonic dystrophy. *Brain* 1998;121:1557-63.
- Mathieu J, Allard P, Porvin P, et al. A 10 year study of mortality in a cohort of patients with myotonic dystrophy. *Neurology* 1999;52:1658-62.
- Mladenovic J, Pekmezovic T, Todorovic S, et al. Survival and mortality of myotonic dystrophy type 1 (Steinert's disease) in the population of Belgrade. *Eur J Neurol* 2006;13:451-4.
- Inoue K, Ogata H, Matsui M, et al. Assessment of autonomic function in myotonic dystrophy by spectral analysis of heart-rate variability. *J Auton Nerv Syst* 1995;55:131-4.
- Hardin BA, Lowe MR, Bhakta D, et al. Heart rate variability declines with increasing age and CTG repeat length in patients with myotonic dystrophy type 1. *Ann Noninv Electrocardiol* 2003;8:227-32.
- Di Leo R, Rodolico C, De Gregorio C, et al. Cardiovascular autonomic control in myotonic dystrophy type 1: a correlative study with clinical and genetic data. *Neuromuscul Dis* 2004;14:136-41.
- Mathieu J, Boivin H, Meunier D, et al. Assessment of a disease-specific impairment rating scale in myotonic dystrophy. *Neurology* 2001;56:336-40.
- Zakrzewska-Pniewska B, Nojszewska M, Przybylowski T, et al. Clinical versus electrophysiological assessment of dysautonomia in obstructive sleep apnea syndrome. *J Clin Neurophysiol* 2004;21:435-9.
- Morris F, Brady WJ, Camm J. *ABC of Clinical Electrocardiology*. 2<sup>nd</sup> ed. Oxford: Blackwell Publishing 2008.
- Drew BJ, Califf RM, Funk M, et al. Practice standards for electrocardiographic monitoring in hospital settings: an American Heart Association scientific statement from councils on cardiovascular nursing, clinical cardiology and cardiovascular disease in the young. *Circulation* 2004;110:2721-46.
- Ewing DJ, Martyn CN, Young RJ, et al. The value of cardiovascular autonomic function tests: 10 years of experience in diabetes. *Diabetes Care* 1985;8:491-8.
- Ewing DJ, Clarke BF. Diagnosis and management of diabetic autonomic neuropathy. *Br Med J* 1982;285:916-18.
- Ewing DJ. Analysis of heart rate variability and other non-invasive tests with special reference to diabetes mellitus. In: Mathias C, Bannister R, editors. *Autonomic failure: a textbook of clinical disorders of the autonomic nervous system*. 3<sup>rd</sup> ed. Oxford University Press 1992, pp. 312-333.
- Schwalm Torsten. *Modern tilt table testing and non-invasive monitoring*. ABW Wissenschaftsverlag 2006.
- Den Heijer JC, Van Dijk JG, Bollen LEM W, et al. Assessment of autonomic function in myotonic dystrophy. *J Neurol Neurosurg Psychiatry* 1991;54:531-4.
- Olofsson BO, Niklasson U, Forsberg H, et al. Assessment of autonomic nerve function in myotonic dystrophy. *J Auton Nerv Syst* 1990;29:187-92.
- Ichikawa K, Kogeyama Y, Fujioka A. Sweating deficiency in myotonic dystrophy. *Rinsho Shinkeigaku* 1989;29:707-12.
- Sakakibara R, Hattori T, Tojo M, et al. Micturitional disturbance in myotonic dystrophy. *J Auton Nerv Syst* 1995;52:17-21.
- Cardani R, Mancinelli E, Saino G, et al. A putative role of ribonuclear inclusions and MBNL1 in the impairment of gallbladder smooth muscle contractility with cholelithiasis in myotonic dystrophy type 1. *Neuromuscul Disord* 2008;18:641-5.
- Ronnbom A, Forsberg H, Danielsson A. Gastrointestinal symptoms in myotonic dystrophy. *Scand J Gastroenterol* 1996;31:654-7.
- O'Brien T, Harper PS, Newcombe RG. Blood pressure and myotonic dystrophy. *Clin Genet* 1983;23:422-6.
- Rakocevic Stojanovic V, Peric S, Paunic T, et al. Cardiological predictors of sudden death in patients with myotonic dystrophy type 1. *J Clin Neurosci* 2012, <http://dx.doi.org/10.1016/j.jocn.2012.09.014>.
- Feargas O'Coilain D, Perez-Terzic C, Reyes S, et al. Transgenic overexpression of human DMPK accumulates into hypertrophic cardiomyopathy, myotonic myopathy and hypotension traits of myotonic dystrophy. *Hum Mol Genet* 2004;13:2505-18.
- Facenda-Lorenzo M, Hernández-Afonso J, Rodriguez-Esteban M, et al. Cardiac manifestations in myotonic dystrophy type 1 patients followed using a standard protocol in a specialized unit. *Rev Esp Cardiol* 2012; <http://dx.doi.org/10.1016/j.recresp.2012.08.011>.
- Petri Helle, Vissing J, Witting N, Bundgaard H, Køber L. Cardiac manifestations on myotonic dystrophy type 1. *Int J Cardiol* 2012;16:82-8.
- McLachlan C, Ocsan R, Spence I, et al. Increased total heart rate variability and enhanced cardiac vagal autonomic activity in healthy humans with sinus bradycardia. *Proc Bayl Univ Med Cent* 2010;23:368-70.
- Zipes DP. Heart-brain interactions in cardiac arrhythmias: a role of autonomic nervous system. *Cleve Clin J Med* 2008;75(Suppl 2): S94-96.
- Hermans MC, Faber CG, Bekerus SC, et al. Structural and functional changes in myotonic dystrophy type 1: a cardiovascular magnetic resonance study. *J Cardiovasc Magn Reson* 2012;14:48.
- Rakocevic-Stojanovic V, Milovanovic B, Ivic N, et al. Cardiac autonomic nervous system in patients with myotonic dystrophy type 1. *Acta Myol* 2007;26:112-4.