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ORIGINAL COMMUNICATION

Hypogonadism in DM1 and its relationship to erectile dysfunction

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Abstract Myotonic dystrophy type 1 (DM1) is characterized by both a premature appearance of age-related phenotypes and multiple organ involvement, which affects skeletal and smooth muscle as well as the eye, heart, central nervous system, and endocrine system. Although erectile dysfunction (ED) is a frequent complaint in patients with DM1, it has not been investigated in great depth. Hypogonadism, which is reported to be one of the physical causes of ED in the general population, frequently occurs in DM1. We planned this case–control study to evaluate the relationship between hypogonadism, as defined by the sexual hormone profile (FSH, LH, testosterone (T) and prolactin) and ED, as assessed by means of an internationally validated self-administered questionnaire (IIEF). DM1 patients had significantly increased mean levels of both gonadotropins (FSH and LH) ($p < 0.0001$) and a reduced mean level of T ($p < 0.0001$) when compared to controls. Twelve patients were eugonadic (normal LH, T, and FSH), while 18 displayed hormonal evidence of hypogonadism, characterized by tubular failure (increased FSH) in all the subjects and associated with interstitial failure in 14 subjects: seven with primary hypogonadism (increased LH and reduced T) and seven with compensated hypogonadism (increased LH and normal T). Patients with hormonal evidence of interstitial failure had a larger CTG expansion ($p = 0.008$), longer disease duration ($p = 0.013$), higher grade of disease ($p = 0.004$) and lower erectile function score ($p = 0.02$) than eugonadic patients. Impotence occurred in 13/14 hypogonadic patients with interstitial failure and in 5/12 eugonadic patients ($p = 0.017$, OR = 18.2).

Keywords Myotonic dystrophy · Erectile dysfunction · Hypogonadism

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Introduction

Myotonic dystrophy type 1 (DM1; OMIM #160900) (Steinert's disease) is the most common muscular dystrophy in adults: its worldwide prevalence has been estimated in 9.1–96.2 $\times$ 10^{-6} [1]. It is an autosomal dominant disorder caused by an expansion of an unstable trinucleotide (CTG) repeat, ranging from 40 to 5,000, in the 3′ untranslated region of the DMPK gene (myotonic dystrophy protein kinase) in chromosome 19q [2]. The pleiotropic expression of the DMPK gene is responsible for the premature appearance of age-related multisystem disorders [3]. Besides being affected by skeletal muscle involvement, EKG abnormalities, presenile cataract, premature balding, brain damage, psychological and vascular changes, patients with DM1 also present hypogonadism, which involves both interstitial (androgenic) and tubular (spermatogenic) gonadic functions [3, 4]. Erectile dysfunction (ED), defined as "the persistent or recurrent inability to achieve and/or maintain a penile erection adequate for satisfactory sexual activity" [5, 6], is reported to be one of the consequences

of androgen deficiency in hypogonadism due to testicular diseases [7, 8], as well as in late-onset hypogonadism in aged men [9].

Taken together, these observations suggest that there is a marked likelihood that ED will occur in DM1. ED, however, remains a poorly studied aspect of the DM1 phenotype. In 2005, we started an investigation of ED in DM1, which showed that impotence occurs in approximately 2/3 of adult DM1 patients, regardless of their age, and that it is associated with changes of orgasmic function, intercourse satisfaction and overall satisfaction [10]. Since androgen replacement therapy is increasingly being used to treat the complications of hypogonadism (i.e., ED) in aging men [11], we planned, in a section of this investigation, a case–control study designed to evaluate the sexual hormones profile in DM1 and to test the role played by interstitial gonadic failure, as expressed by testosterone-luteinizing axis functioning, in ED in DM1. In this paper, we present the results of this section of the study.

Patients and methods

Study population sampling

As described in our previous paper [10], the series of DM1 male patients (age 18–60 years) under clinical surveillance in our neuromuscular clinic on January 1, 2005, were asked to give their informed consent to participate in this study. Besides an evaluation of ED, the study also included the measurement of sexual hormone levels. The clinical diagnosis of DM1 was genetically confirmed in all the patients on the basis of the CTG expansion in DNA obtained from peripheral blood leukocytes. Disease severity was evaluated according to the muscular impairment rating scale for myotonic dystrophy (MIRS) [12]. Age at disease onset was retrospectively determined on the basis of the appearance of the myotonic phenomenon. All the patients were clinically evaluated for any disease or medication and tested with both the Mini-Mental State Examination and Hamilton Depression Rating Scale (HAM-D). Diseases, surgery, or medication that were known to interfere with sexual life, erectile function, and sexual hormone levels were considered exclusion criteria, as were congenital DM1, cognitive dysfunction, and HAM-D "severe" or "very severe" scores. Consequently, four patients with congenital DM1, one patient with polyneuropathy, nine patients with diabetes/glucose intolerance or hypertension, and three patients with depression were excluded from the study. One patient refused to undergo the sexual hormone study. Thus, 30 eligible patients underwent both the sexual hormone and ED tests. The volume of the patients' testicles was not measured.

Thirty age-matched (±1 year) healthy subjects, selected from our working environment, also underwent the sexual hormone and ED tests.

The hormonal study was performed at the same time as the erectile function study in all the subjects.

Erectile function evaluation

Erectile function was evaluated by means of the internationally validated index of erectile function (IIEF) [13]. The IIEF is a widely used, multi-dimensional, self-report instrument for the evaluation of male sexual function that has been adopted as the 'gold standard' measure for impotence [14] and has been recommended as a primary endpoint for clinical trials of ED as well as for the diagnostic evaluation of its severity [15]. It explores five domains of male sexual function, i.e., erectile function (frequency, firmness and confidence of erection, penetration ability, ability and frequency of maintenance), intercourse satisfaction (frequency, satisfaction, and enjoyment of intercourse), orgasmic function (frequency of ejaculation and orgasm), sexual desire (frequency and level of sexual desire) and overall satisfaction (overall and relationship satisfaction). For the purposes of this study, we considered, in particular, the "erectile function" domain of IIEF (Q1, Q2, Q3, Q4, Q5 and Q15), whose total score identifies patients with ED (score < 25) and without ED (score ≥ 25).

Sexual hormone assay

Fasting morning blood samples, collected from patients between 08.00 and 09.00 a.m. from an antecubital vein, were centrifuged after 30 min and the serum was immediately frozen at −20°C. Serum follicle stimulating hormone (FSH), luteinizing hormone (LH), prolactin (PRL), and testosterone (T) were measured in duplicate with chemiluminescent microparticle immunoassay (CMIA, Architect System) (Abbott Laboratories, IL, USA), with detection limits of 0.05 U/l, 0.07 U/l, 0.6 ng/ml and 0.28 nmol/l, respectively; intra- and inter-assay coefficients of variation for our laboratory were: 2.9 and 3.7% at 4.1 U/l (FSH); 3.2 and 4.6% at 3.7 U/l (LH); 3.5 and 4.2% at 5.8 ng/ml (PRL); 2.3 and 3.8% at 13.7 nmol/l (T).

The normal ranges of the sexual hormone tests in male subjects aged 18–60 years determined in our laboratory by evaluating 150 normal male subjects were: FSH 1.32–9.72 UI/l; LH 1.72–8.16 UI/l; PRL 2.42–16.37 ng/ml; T 9.60–39.85 nmol/l.

Statistical analysis

Both the hormonal values and scores of erectile function domain of IIEF of patients and controls were compared.

The clinical, genetic, and hormonal characteristics of patients with ED and those without ED were also compared.

To define the patients' gonadal hormone profile and to test its relationship to both the clinical and genetic characteristics, as well as with the occurrence of ED, the patients' hormonal gonadal status was classified in one of three categories according to the gonadotropin and T levels: (a) eugonadism (normal gonadotropins and T); (b) hypogonadism with hormonal evidence of interstitial failure, which includes primary hypogonadism (high LH and low T) and compensated hypogonadism (high LH and normal T) [16]; (c) hypogonadism without hormonal evidence of interstitial failure (high FSH, normal LH, and T).

Statistical analysis was performed with the use of the Chi-square test for categorical variables, Student's *t* test for continuous variables with normal distribution and non-different variance (as evaluated by Levene test), Mann–Whitney *U* test and Kruskal–Wallis test for variables with non-normal distribution and significantly different variance (as evaluated by Levene test). Two-sided *p* values were calculated for all the analyses; values of 0.05 or less were considered to indicate statistical significance.

Data were analyzed with SPSS software for Mac, version 16.0.

Results

The demographic and clinical characteristics of the patients included in the study are shown in Table 1. All the patients stated that they were engaged or married. The control subjects' age ranged between 21 and 60 years, while their mean age was 43.2 years (SD = 11.5 years).

Table 1 Demographic and clinical characteristics of 30 DM1 patients included in the study

	Mean (SD)	Median (IQR)	Range
Age (years)	44.7 (13.1)	48 (37–55.5)	20–60
Age onset (years)	26.5 (14.0)	19 (16–36)	13–58
Disease duration (years)	18.4 (13.0)	18.5 (6.5–31)	2–42
CTG (*n*)	366.5 (213.6)	365 (172.5–563.7)	60–730
Disease severity (MIRS)	2.77 (0.9)	3 (2–4)	1–4

The IIEF showed that erectile function scores of patients were significantly lower than those of controls ($p = 0.001$) (Table 2). Impotence, as defined by a low score (<25) in the erectile function domain of the IIEF, occurred in 21 patients (70%) and five controls (16.7%) (OR = 11.66; 95% CI 3.3–40.2; $p < 0.001$).

The sexual hormone evaluation showed that DM1 patients had significantly higher mean levels of both gonadotropins (FSH and LH) ($p < 0.0001$) and a lower mean T level ($p < 0.0001$) than controls. The mean PRL level in DM1 was also higher in patients than in controls, though the difference did not reach statistical significance (Table 2). When we considered the hormone levels in each subject, we found that 18 patients (60%) had an increased FSH level, 14 (46.6%) had an increased LH level, seven (23.3%) had a reduced T level, and three (10%) had an increased PRL level; by contrast, the hormone levels in all the control subjects fell within the normal range.

The sexual hormone changes, which were partially superimposed, allowed different categories of patients to be distinguished (Fig. 1). Twelve patients displayed hormonal evidence of eugonadism (normal LH, T and FSH), while the remaining 18 displayed hormonal evidence of hypogonadism. All the subjects in the latter group displayed hormonal evidence of tubular failure (increased FSH), which was associated with hormonal evidence of interstitial failure in 14 subjects, seven of whom displayed the characteristics of primary hypogonadism (increased LH and reduced T) and the remaining seven those of compensated hypogonadism (increased LH and normal T).

The analysis of the demographic and clinical characteristics of the patients in relation to ED showed that the age of the patients with ED and of those without ED was similar. By contrast, patients with ED had a larger CTG expansion ($p = 0.007$), younger age at disease onset ($p = 0.007$), longer disease duration ($p = 0.0001$), higher grade of disease severity ($p = 0.001$), increased levels of LH ($p = 0.0001$), reduced levels of T ($p = 0.036$), and increased levels of FSH ($p = 0.001$). PRL levels in patients

Table 2 Hormone levels and erectile function scores in 30 DM1 patients and 30 healthy controls

	Patients ($n = 30$)			Controls ($n = 30$)			*p*	Normal range
	Mean (SD)	Median (IQR)	Range	Mean (SD)	Median (IQR)	Range		
LH (U/l)	9.43 (6.5)	7.28 (3.94–13.65)	2.79–25.10	3.86 (1.6)	3.56 (2.60–4.75)	1.78–7.95	0.0001	1.72–8.16
T (nmol/l)	13.95 (6.9)	13.52 (9.63–19.03)	2.88–29.41	25.77 (9.8)	26.21 (15.07–34.30)	10.28–39.80	0.0001	9.60–39.85
FSH (U/l)	16.75 (14.4)	13.86 (5.20–22.87)	1.5–60.1	4.31 (1.9)	4.12 (2.77–5.32)	1.60–8.80	0.0001	1.32–9.72
PRL (ng/ml)	10.31 (7.9)	8.65 (6.26–10.02)	3.88–45.66	7.77 (3.4)	7.55 (4.34–9.88)	2.96–15.20	n.s.	2.42–16.37
Erectile function score	18.10 (8.9)	20 (11.75–26)	2–30	27.4 (3.4)	29 (26–30)	17–30	0.0001	25–30

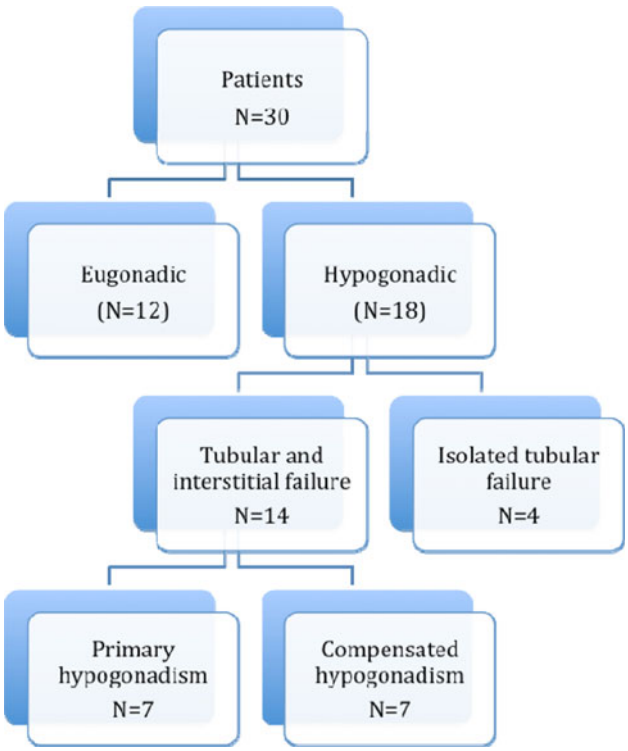

Fig. 1 Sexual hormone profile in 30 male patients with DM1

with ED and in those without ED were not different (Table 3). Patients with severe grades of disease (MIRS 3–4) had a significantly higher frequency of ED than patients with MIRS 1–2 (OR = 20; 95% CI = 2.03–196.37; $p = 0.01$).

The analysis of the patients' characteristics in relation to their hormone profile (hypogonadism with interstitial failure, hypogonadism without interstitial failure and eugonadism) revealed a significant difference in the CTG expansion ($p = 0.028$), disease duration ($p = 0.027$), disease severity ($p = 0.015$) and erectile function ($p = 0.049$). Pairwise comparison showed that hypogonadic patients with interstitial failure had a larger CTG expansion ($p = 0.008$), longer disease duration ($p = 0.013$), higher MIRS grade ($p = 0.004$), and lower ED score ($p = 0.02$) than eugonadic patients. Hypogonadic patients without interstitial failure had a larger CTG expansion than eugonadic patients ($p = 0.02$), and shorter disease duration (0.046) than patients with interstitial failure (Table 4).

ED occurred in 13/14 hypogonadic patients with interstitial failure (7/7 of patients with primary hypogonadism and 6/7 patients with compensated hypogonadism), in 3/4 hypogonadic patients without interstitial failure and in 5/12 eugonadic patients ($p = 0.017$). Patients with hormonal evidence of interstitial failure displayed a significantly higher risk of developing ED than eugonadic patients (OR = 18.2; 95% CI 1.7–188.0; $p = 0.015$).

Discussion

Epidemiological studies in the general population suggest that 5–20% of men have moderate to severe ED [17] and that both the prevalence and severity of ED increase with age, which is an independent risk factor for this disorder [5, 18]. However, population studies stress the relevance of both physical and psychological factors, other than age, in the etiology of ED. In particular, vascular, neurological, and hormonal diseases are reported to be major organic causes of ED, respectively occurring in 60–80, 10–20, and 5–10% of cases of impotence [6].

Impotence is a symptom that has not received much attention in DM1, despite being a frequent complaint in patients with this disease. In keeping with previous reports [10], ED, in various degrees of severity, occurred in approximately 2/3 of the DM1 patients in this study. The occurrence of ED was independent of the age of patients, but was correlated with other factors intrinsic to DM1, such as disease duration and severity and CTG expansion. Moreover, on the basis of the selection criteria adopted in

Table 3 Clinical characteristics and hormone levels in DM1 patients with and without ED

Variables	Patients with ED ($n = 21$)			Patients without ED ($n = 9$)			p
	Mean (SD)	Median (IQR)	Range	Mean (SD)	Median (IQR)	Range	
Age (years)	45.6 (12.6)	49 (41–56)	20–60	42.8 (14.7)	47 (27–56.5)	22–60	n.s.
CTG (n)	433.4 (199.2)	440 (272.5–595.5)	96–730	210.6 (164.8)	120 (100–300)	60–575	0.007
Age-onset (years)	21.8 (10.5)	18 (15.5–22.5)	13–55	37.3 (15.7)	39 (20–51.5)	16–58	0.007
Disease duration (years)	24.0 (11.5)	25 (14–33.5)	2–42	5.4 (2.7)	5 (3–7.5)	2–10	0.0001
Disease severity (MIRS)	3.14 (0.8)	3 (2–4)	1–4	1.89 (0.6)	2 (2–2)	1–3	0.001
LH (U/l)	11.76 (6.4)	9.87 (6.29–16.16)	3.35–25.1	4.02 (1.9)	3.24 (2.96–4.03)	2.79–9.04	0.0001
T (nmol/l)	12.00 (5.8)	12.88 (5.45–16.84)	2.88–22.88	18.52 (7.4)	19.27 (10.87–25.52)	9.72–29.41	0.036
FSH (U/l)	21.32 (14.8)	16.1 (10.41–34.15)	3.25–60.1	6.09 (5.2)	4.37 (2.99–7.88)	1.5–18.24	0.001
PRL (ng/ml)	9.44 (5.1)	8.56 (5.93–10.69)	3.88–24.15	12.33 (12.6)	8.74 (6.91–10.06)	6.13–45.66	n.s.

Table 4 Clinical characteristics and erectile function score in relation to hormone profile in 30 DM1 patients

Variables	Hypogonadism with interstitial failure ($n = 14$)			Hypogonadism without interstitial failure ($n = 4$)			Eugonadism ($n = 12$)			p^a
	Mean (SD)	Median (IQR)	Range	Mean (SD)	Median (IQR)	Range	Mean (SD)	Median (IQR)	Range	
Age (years)	49.4 (9.9)	51 (42.75–57.25)	23–60	34.5 (11.3)	34 (24–45.5)	23–47	42.8 (15.2)	48 (25–55)	20–60	n.s.
CTG (n)	456.9 (203.9)	420 (330–685)	96–730	488.75 (133.3)	532.5 (347.5–586.25)	300–590	220.4 (165.1)	170 (100–268.75)	60–600	0.028
Age at onset (years)	23.4 (12.1)	18 (16–27.5)	14–55	21.25 (12.1)	16.5 (13.25–34)	13–39	31.75 (15.9)	25.5 (19–49.75)	15–58	n.s.
Disease duration (years)	25.9 (11.6)	26.5 (21–35.5)	2–42	13.25 (6.2)	11.5 (8.5–19.75)	8–22	11.4 (11.8)	6 (3.25–21.25)	2–35	0.027
Disease severity (MIRS)	3.36 (0.7)	3.5 (3–4)	2–4	2.50 (0.6)	2 (2–3)	2–3	2.17 (0.93)	2 (2–2)	1–4	0.015
Erectile function score	16.07 (7.0)	14.5 (12–21.25)	2–29	11.50 (12.2)	7 (3–24.5)	3–29	22.67 (8.0)	25.5 (19.5–28)	4–30	0.049

Pairwise comparison of groups of cases (Mann–Whitney U test): significantly different variables and level of significance

Hypogonadism with interstitial failure versus eugonadism: CTG ($p = 0.008$); disease duration ($p = 0.013$), disease severity ($p = 0.004$), erectile function score ($p = 0.02$)

Hypogonadism without interstitial failure versus eugonadism: CTG ($p = 0.02$)

Hypogonadism with interstitial failure versus hypogonadism without interstitial failure: disease duration ($p = 0.046$)

[a] Significantly different variables and level of significance in the comparison of the three groups of cases (Kruskal–Wallis test)

this study, we rule out that physical factors other than those intrinsically related to the disease itself contributed to the pathogenesis of ED in our sample.

The pleiotropic expression of the DMPK gene in DM1 is responsible for the premature expression of typical age-related phenotypes, among which ED may be included. However, other factors that are unrelated to premature aging may be involved in the occurrence of impotence in DM1. Indeed, the misplicing of target gene transcripts, which produces the typical multiple organ involvement in the DM1 phenotype, may be the cause of anatomical and functional changes in the complex mechanisms of penile erection, which is influenced and regulated by biological (local, cardiovascular, neuronal, and hormonal) as well as psychological and lifestyle factors.

In this study we focused on hypogonadism, and in particular on interstitial dysfunction, whose symptoms include ED. In keeping with reports by other investigators [3, 4], we found that 46% of our patients displayed hormonal evidence of interstitial gonadic failure, in the form of either primary hypogonadism (increased LH and reduced T) or of compensated hypogonadism (increased LH and normal T) [16].

Both primary and compensated hypogonadism are related to LH-T axis dysfunction and express, in varying degrees of severity, Leydig cell involvement. Interstitial gonadic failure in our sample was accompanied by hormonal evidence of tubular failure (FSH increase) in 60% of our patients, which is in keeping with pathological evidence that testicle abnormalities in DM1 involve both interstitial and tubular function. In accordance with the literature, in which testicular atrophy is reported to be the most prominent feature in approximately 80% of DM1 patients, we routinely observed both testicular hypotrophy and oligozoospermia in our DM1 patients (data not shown). Histological studies have confirmed that the testicles of DM1 patients are characterized by an increase in the number and size of Leydig cells, as well as by tubular atrophy, hyalinization, and fibrosis of the seminiferous tubules and reduced spermatogenesis [3, 19]. These structural gonadic changes correlate with endocrine findings [3, 19, 20], which point to markedly increased FSH levels, moderately increased or normal LH levels and moderately reduced T levels in male patients [21]. These results reflect findings in patients with generalized testicular failure, such as those with Klinefelter disease (XXY), in whom serum T levels are in the low or low-normal range and serum gonadotropins are subsequently overproduced [22], as well as in aging men, in whom hypogonadism is characterized by increased LH levels and reduced or normal T levels (primary and compensated hypogonadism) [16], along with progressively impaired spermatogenesis. Although the changes in interstitial and tubular function are frequently

associated in hypogonadism, the hormonal regulation of erectile function is primarily directed by the LH-T axis. When we compared the endocrine findings with the occurrence of ED, we found that impotent patients had significantly lower T levels and significantly higher LH levels. Moreover, the IIEF revealed significantly lower erectile function scores in patients with hormonal evidence of interstitial failure than in eugonadic patients. In particular, ED was associated with hormonal evidence of LH-T axis dysfunction in 43.3% of the DM1 patients, while 62% of patients with ED displayed hormonal evidence of primary or compensated hypogonadism. To sum up, as observed in other gonadic diseases characterized by a Leydig cell dysfunction, hypogonadism with interstitial failure seems to play a role in the pathogenesis of ED in DM1. However, our data also show that the hormone profile is correlated with both the clinical and genetic characteristics of the patients. In particular, a larger CTG expansion, a longer disease duration and a higher MIRS grade characterize the group of patients with interstitial gonadic failure. On the basis of these findings, we may assume that the role of Leydig cell dysfunction in the pathogenesis of ED in DM1 is likely to be regulated by a number of complex mechanisms related to both genetic (CTG expansion) and clinical (disease duration and severity) factors. In particular, it may be hypothesized that Leydig cell dysfunction, like other phenotypic characteristics in DM1, is regulated by CTG expansion and undergoes a progression that is comparable to that of muscle involvement. On the other hand, we detected a substantial prevalence of eugonadic patients with ED (16.6%), which leads us to hypothesize that factors other than interstitial gonadic function involved in the complex mechanism of penile erection (e.g., hemodynamic regulation, smooth muscle cell function in the cavernous bodies, central nervous system control of the switch between muscle contraction and relaxation, sympathetic and parasympathetic nerve activity, regulation of the activation of biochemical events that induce cavernous smooth cell relaxation [23]) play a pathogenetic role in ED in DM1.

Interesting therapeutic considerations arise from the possible relationship between hypogonadism and ED in DM1. Indeed, a marked drop in T concentrations in men usually results in failure of both libido and erectile function [24], and, although attempts to clarify the relationship between the decline in circulating T and aging ED have not yielded any significant findings [7], an increasing number of symptomatic older men are being considered for androgen replacement therapy [11].

On the basis of these data, we hypothesize that T supplementation may be useful in the treatment of ED in DM1. Testosterone has already been tried in muscular dystrophy and, in particular, in DM1. Experimental trials, in which sexual function was not however tested, have shown that weekly T administration in DM1 increases the muscle protein synthesis rate in DM1 [25] as well as the basal metabolic rate and lean body mass in healthy men and in men with muscular dystrophy (DM1, facioscapulohumeral and limb girdle dystrophy) [26], but has no effect on muscle strength in DM1 [27]. Moreover, the use of T to enhance strength and muscle mass has been considered not only in hypogonadal [28] and aging men [29] but also in glucocorticoid induced myopathy [30, 31] and in HIV and cancer-related skeletal muscle loss and wasting [32, 33]. Lastly, the effect of oxandrolone, a synthetic dehydroepiandrosterone derivative, has been investigated in dystrophynopathies and inclusion body myositis [34, 35]. More recently, the use of T supplementation was proposed in a clinical study in which a high incidence of hypogonadism was observed in men with various types of myopathies, such as facioscapulohumeral dystrophy, inclusion body myositis, dystrophynopathy, and metabolic myopathy, as well as DM1 [36].

In conclusion, in keeping with studies on other diseases characterized by hypogonadism with interstitial failure, such as Klinefelter disease [37], we suggest that DM1 patients with overt or compensated interstitial hypogonadism (low/normal T and high levels of LH) may be considered suitable candidates for T supplementation. Although T supplementation is, on the basis of the results of a previous randomized trial [27], unlikely to have a therapeutic effect on muscle strength in DM1, it should be considered to treat ED as it may improve the sexual life in such patients. Further studies are warranted to investigate the potential utility of T supplementation in the sexual life of DM1 patients.

Strengths and limitations of the study

This is, to our knowledge, the first case–control study conducted to evaluate the relationship between hypogonadism and ED in DM1. There are, however, some limitations that need to be highlighted. It is evident that ED derives from multiple and concomitant pathogenetic factors. Although we excluded patients with diseases or clinical conditions that are known to interfere with sexual life, the intrinsic multisystem involvement of the disease limits the possibility to weight the effect of hypogonadism alone on the pathogenesis ED. The enrolment of a larger cohort of patients would allow the statistical analysis of the results to highlight which factors independently influence the occurrence of ED. In our sample of patients, we detected a marked difference in disease duration between patients with and those without ED, as well as in patients with and those without hypogonadism. Given the cross-sectional design of the study, it was not possible to determine the

directional or temporal nature of the relationships we observed, for which prospective data are needed.

Conflict of interest None.

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