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Resistance training in women with myotonic dystrophy type 1: a multisystemic therapeutic avenue

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ABSTRACT

Myotonic dystrophy type 1 (DM1) is a hereditary disease characterized by muscular impairments. Fundamental and clinical positive effects of strength training have been reported in men with DM1, but its impact on women remains unknown. We evaluated the effects of a 12-week supervised strength training on physical and neuropsychiatric health. Women with DM1 performed a twice-weekly supervised resistance training program (3 series of 6–8 repetitions of squat, leg press, plantar flexion, knee extension, and hip abduction). Lower limb muscle strength, physical function, apathy, anxiety and depression, fatigue and excessive somnolence, pain, and patient-reported outcomes were assessed before and after the intervention, as well as three and six months after completion of the training program. Muscle biopsies of the *vastus lateralis* were also taken before and after the training program to assess muscle fiber growth. Eleven participants completed the program (attendance: 98.5 %). Maximal hip and knee extension strength ($p < 0.006$), all One-Repetition Maximum strength measures ($p < 0.001$), apathy ($p = 0.0005$), depression ($p = 0.02$), pain interference ($p = 0.01$) and perception of the lower limb function ($p = 0.003$) were significantly improved by training. Some of these gains were maintained up to six months after the training program. Strength training is a good therapeutic strategy for women with DM1.

1. Introduction

Myotonic dystrophy type 1 (DM1) is an autosomal dominant disorder and the most common form of muscular dystrophy in adults [1]. This disease is more prevalent in the Saguenay–Lac-Saint-Jean region, Quebec, Canada, where one affected individual per 633 people is found, compared approximatively to one per 5500 elsewhere [1,2]. DM1 is caused by an abnormal repetition of CTG nucleotide triplet in the *dystrophia myotonica protein kinase* (*DMPK*) gene [3]. This repetitive sequence results in the accumulation of toxic mRNA in the nucleus, inducing transcriptomic dysregulation such as splicing defects. It has been established that the downregulation of muscle-blind-like protein 1 (MBNL1) and the upregulation of CUG-binding protein 1 (CUGBP1), two RNA-binding proteins, lead to various multisystemic impairments [4]. Clinical manifestations include several signs and symptoms, such as myotonia, muscle weakness, muscle wasting, excessive fatigue, somnolence, and apathy [3]. The severity of the disease differs according to the phenotype (congenital, infantile,

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juvenile, adult, and late-onset), which is determined by the number of CTG repeats and the age at symptom onset [4]. Clinical manifestations also vary between sexes. For example, women tend to present more somnolence and pain than men [5,6]. In addition, quantitative measurement of strength over 9 years revealed that men showed a significantly greater rate of decline in muscle strength than women [7].

Muscle weakness and muscle atrophy, particularly the atrophy of type I myofibers, are cardinal symptoms of this disease [3]. DM1 is clinically interpreted as a model of premature aging [8]. Depending on the lower limb muscle group assessed, individuals with DM1 gradually lose 30.3 % to 54.5 % of their residual maximal strength over nine years, with a pattern of weakness progression from distal to proximal [7]. Muscle weakness in the lower limbs, along with fatigue, are reported as the main explanatory factors of disrupted social participation in the domains of housing, mobility, employment, and recreation [9]. Also, variability in the performance at the 10 Meter Walk test (10mWT), Timed Up & Go (TUG), and Berg Balance Scale (BBS) is mostly explained by muscle weakness of knee extensors and ankle dorsiflexors [10]. Among non-muscular symptoms, apathy, fatigue, and daytime sleepiness are frequently reported with prevalence rates of 40–55 % [11,12], 90.8 % [13] and 87.9 % [13], respectively. Fatigue and mobility limitations have been reported to significantly impact the quality of life of affected people [13]. Chronic pain is also reported in 84 % of patients with DM1, which is even more prevalent (71 % of men vs. 96 % of women) and severe (42 % of women had severe pain vs. 20 % of men) in women [6]. One study hypotheses that nociceptive pain may likely be due to poor muscle tissue quality [6]. Additionally, pain in DM1 may also stem from neuropathic factors [6].

There is still no cure for DM1. However, muscle strengthening holds great potential to improve this multisystemic condition. Indeed, a recent study carried out on a cohort of 11 men with DM1 who have undergone a 12-week lower limb strength training program has shown clinical and molecular positive effects [14–18]. Briefly, these men increased their lower limb muscle strength and physical capacity. Also, they reduced their perception of apathy, fatigue and daytime sleepiness. Some of those clinical gains were even maintained up to 6 months after the end of the training program. Additionally, this training program increased the size of type I and type II muscle fibers in a sub-group of participants [14]. Furthermore, gene expression and splicing defects were rescued after the training program [16], along with mitochondrial content [18]. Similarly, it has been recently shown that aerobic training rescued mitochondrial dysfunction in individuals (men and women) with DM1 [19]. One could speculate that the strength training program carried out in the men DM1 cohort would lead to comparable results in women with DM1. However, in a similar population of elderly, men showed a greater increase in knee extensor maximal torque and muscle quality than women following a resistance training program [20]. Moreover, the differences in clinical manifestations severity and progression across sexes in DM1 [5,7] reinforce the need to address this unanswered question. Thus, this study aimed to assess the impact of a 12-week lower limb supervised resistance training program on lower limb muscle strength, physical function, neuropsychiatric manifestations and myofiber size in women with DM1.

2. Materials and methods

2.1. Recruitment

Participants were DM1 patients followed at the neuromuscular clinic of the *Centre intégré universitaire de santé et de services sociaux* (CIUSSS) du Saguenay–Lac-Saint-Jean, Quebec, Canada. The clinical team obtained their permission to be contacted by the research team before their enrollment. The inclusion criteria were to: 1- have a genetically confirmed diagnosis of DM1 (juvenile, adult, or late onset), 2- be a woman between 20 and 60 years old, 3- have the consent of their neurologist who carefully reviewed the list of health conditions leading to exercise restriction (Appendix 1), and 4- be able to provide informed consent. The study was approved by the *Ethics Review Board* of the CIUSSS du Saguenay–Lac-Saint-Jean (Quebec, Canada) and each participant provided written consent.

2.2. Procedure

Assessments were performed at five time points as illustrated in Fig. 1. T0, T1 and T2 assessments were respectively done before, in the middle of, and after the training program. T3 and T4 were done three and six months after the end of the training program. Muscle biopsies were collected in each participant before (T0) and after the end of the training program (T2).

2.3. Resistance training program

The 12-week training program was previously followed by a cohort of 11 men with DM1 [14]. It involved twice-weekly supervised training sessions at the gym of the University of Quebec at Chicoutimi, including five lower limb exercises (leg extension, leg press, hip abduction, squat, and plantar flexion). The plantar flexion exercise was adapted to the participant's ability, either unipodal or bipodal with a Smith machine's guided bar, or seated with free weights. The squat exercise was executed with a Smith machine's guided bar, and an adapted exercise of squat or sit-to-stand was given to participants who could not squat safely. Leg extension, leg press, and hip abduction were done with exercise gym machines. Each training session started with a 5-minute warm-up on a bike at low to moderate intensity, followed by three sets of 6 to 8 repetitions of each lower limb exercise with a 2-minute rest between sets. The appropriate weights were determined during the first session with Epley's formula: $\textit{One Repetition Maximum}\,(1RM) = W(1 + \frac{R}{30})$, where W= lifted weight and R= number of repetitions [21]. Then, 6RM and 8RM were calculated to estimate the appropriate weight needed to ensure that participants execute 6 to 8 repetitions. During subsequent sessions, if the participant could complete more than 8 repetitions, weight was increased by 10 % till the participant did not exceed 8 repetitions. On the contrary, the weight was decreased following the same procedure. Also, 1RM was assessed after 6 and 12 weeks of training as a measure of progression (Fig. 1). The 1RM of the plantar flexion exercise was not included in the analyses due to the large variations in exercise execution (unipodal vs. bipodal) among participants. All training sessions were supervised by either trained physiotherapy students (RB, M-ELL, DT, MR) with a kinesiologist (SEB) or a physical therapist (LGC). To ensure adherence to the training program, participants were trained in pairs and contacted each Sunday to confirm their availability for the upcoming week. If necessary, an alternate appointment was scheduled for the same week at their convenience while having at least one day of rest between training sessions.

2.4. Clinical measurements

All outcome measures were assessed using standardized operating procedures to ensure consistency. Most of the clinical measurements were highly reliable and were conducted as previously published [14,22–24]. Clinical and anthropometric measurements were performed by trained physical therapists

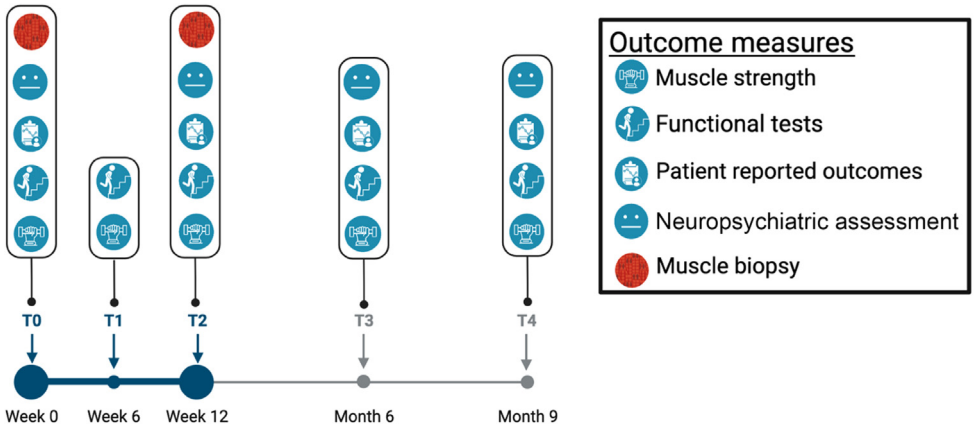

Fig. 1. Study design.

(MM or LGC). The number of CTG repeats and phenotypes were extracted from medical files.

2.4.1. Muscle strength

The maximal isometric muscle strength (MIMS) of lower limbs was assessed using quantified muscle testing with a standardized protocol using a push-pull MEDup^{tm} handheld dynamometer (Atlas Medic, Québec, Canada) [25,26]. Two trials for each left and right leg were executed for the following muscle groups: hip abductors, hip extensors, hip flexors, knee extensors, knee flexors and ankle dorsiflexors. If the difference between the two trials was greater than 10 %, a third trial was done and the mean of the two closest measurements was used for analysis. Afterward, the strength of each muscle group was calculated as the mean of the right and left sides. The assessment schedule was as follows: T0 and T2: all muscle groups; T1: knee extensors only; T3 and T4: knee and hip extensors only. MIMS has shown excellent inter- and intra-rater reliability (ICC = 0.95) in a healthy population [26]. Also, it has shown good validity and inter-rater reliability (ICC = 0.98) for knee extensors in men with DM1 [22]. As previously mentioned, 1RM of each exercise was assessed and calculated using Epley's formula [21] at each time point. Modified exercises, such as plantar flexion seated and modified squat were not kept for further analysis due to too high variability in the execution form.

2.4.2. Functional tests

Walking speed at both comfortable and maximal paces was assessed using the 10 Meter Walk Test (10mWT). Participants were asked to walk at their comfortable and maximum pace along a 14-meter hallway, which included a 2-meter distance acceleration and deceleration zones before and after. The time taken to walk the 10-meter distance was recorded. The 10mWT has demonstrated good reliability (ICC = 0.99) [27] and construct validity in DM1, with a minimal clinically important difference (MCID) of 13 % [24].

The 30-second sit-to-stand (30 sSTS) test was used to measure the lower limb functional strength. Participants were asked to rise from a standard armless chair to a full standing position (hips and knees extended), as many times as possible in 30 s, without using their arms for support. Two or three trial repetitions were allowed to ensure proper comprehension of the test and the correct execution. If the 30-second mark was reached before one full repetition was completed, it was counted only if more than half of it was completed. The mean of two trials was calculated for analysis. This test showed good reliability in the DM1 population (ICC = 0.96) [27].

The 10-step timed stair test (10TST) was conducted to measure the time taken to climb ten standard stairs at both comfortable and maximal paces. The time taken to ascend and then descend the stairs was recorded. Additionally, the method of climbing the stairs (alternating or not) and the use of handrails (0, 1, or 2) were noted [28].

The Timed Up & Go (TUG) was used to assess functional mobility [29]. Participants were asked to stand up from a chair, walk 3 m at a comfortable pace, turn around, walk back to the chair, and sit down. The mean time of three trials was recorded for analysis. This test has been shown to have good intra-rater reliability (ICC = 0.83) [30] and validity in the DM1 population [24].

2.4.3. Neuropsychiatric assessment

The level of apathy was assessed using the clinician's French version of the Apathy Evaluation Scale (AES-C), which contains subscales for behavior, cognition and emotion dimensions [31]. The maximum score is 72, where a higher score represents more severe apathy. The AES-C has demonstrated excellent internal consistency in individuals with DM1 (Cronbach's Alpha = 0.87) [32].

Anxiety and depression were assessed using the Hospital Anxiety and Depression Scale (HADS) [33]. This self-administered scale consists of 14 items with two subscales, one for each anxiety and depression domain. Each domain is reported on a total of 21 and a higher score represents a higher level of psychological distress.

Fatigue and daytime sleepiness were assessed by the Fatigue and Daytime Sleepiness Scale (FDSS). The total score is reported on 24 and a higher score represents a higher severity of fatigue and daytime sleepiness. This 12-item questionnaire was specifically developed for the DM1 population and showed good psychometric properties [34,35].

2.4.4. Patient-reported outcomes

All questionnaires were completed with the help of a physical therapist (LGC or MM) by reading the questions to the participant and providing clarifications when needed.

2.4.4.1. DM1-activ. The DM1-activ questionnaire was used to assess the impact of the disease on social participation, and it was designed explicitly for the DM1 population [36]. The total score ranges from 0 to 40, with higher scores indicating a greater impact of the disease on the participant's participation in daily and social activities.

2.4.4.2. Lower extremity functional scale (LEFS). The LEFS questionnaire was used to assess lower limb functions in performing daily activities [37]. This 20-items scale has a

maximum score of 80 points, with lower scores indicating higher lower limb impairments [37].

2.4.4.3. Brief pain inventory (BPI). The BPI was used to assess the severity of pain and its interference with general activities, mood, walking, work, relationships, sleep, and enjoyment of life. Each item is rated on a 0 to 10 Likert scale, where a higher score indicates more intense pain and more significant interference [38].

2.4.4.4. Falls. Participants were asked about how many times they fell in the last week and month.

2.4.4.5. Self-reported changes and perceptions. During the training program, any changes reported by the participants were recorded in a training program log. After the training program, participants were asked to report the most significant changes perceived in their daily lives induced by the training program.

2.4.4.6. Acceptability. A discussion group was conducted at the end of the training program to gather participant's feedback on the intervention, including facilitators and barriers to adherence to the training program. The discussion group was led by a physical therapist (LGC) using an interview guide developed according to the framework developed by Sekhon et al. [39] and adapted to the current intervention.

2.4.4.7. Life habits changes. At the follow-up visits, participants were asked if they practiced physical activity in the last month. If yes, the type and frequency were noted.

2.5. Muscle biopsy procedure

Muscle biopsies were performed according to previously described procedures [14]. Briefly, muscle biopsies were obtained from the *vastus lateralis* muscle (from an incision at 15 cm above the patella) within one week before and after the 12-week training program (Fig. 1). Biopsies were obtained using a Bergström muscle needle under local anesthesia with 2 % xylocaine. After extraction, the incision was closed with a 4.0 silk suture, and participants were instructed about proper post-biopsy care. A piece of each fresh muscle tissue was mounted in tragacanth and other pieces of muscle tissue were flash-frozen in liquid nitrogen; both were stored at −80 °C until further use.

2.5.1. Triple myosin heavy chains immunostaining (3MHC)

Muscle tissues were cut into cross-sections of 10 µm, and slides were stored at −80°C until immunostaining. To assess muscle fiber type and size, cross-sections were immunolabeled for myosin heavy chains (MHC) type I (slow-twitch) and II (fast-twitch). First, the slides were thawed at room temperature. Then, cross-sections were washed thrice with PBS and blocked for 30 min with goat serum (10 %) and PBS. Next, they were incubated at room temperature for 1 h with primary antibodies: mouse IgG2b anti-MHC type I (BA-F8, 1:25), mouse IgG1 monoclonal anti-MHC type IIa (SC-71, 1:200), mouse anti-MHC type IIx (6H1, 1:25) and rabbit IgG polyclonal anti-laminin (Sigma L9393, 1:750). After this step, the cross-sections were washed three times with PBS and incubated for 1 h at room temperature with the secondary antibodies: Alexa Fluor 350 IgG2b (y2b) goat anti-mouse (Invitrogen, A-21,140, 1:500), Alexa Fluor 594 IgG1 (y1) Goat anti-mouse (Invitrogen, A-21,125, 1:100), Alexa Fluor 488 IgM goat anti-mouse (Invitrogen, A-21,042, 1:500) and Alexa Fluor 488 IgG goat anti-rabbit (A-11,008,1:500). Finally, the slides were washed three times with PBS and mounted with a coverslip and Prolong Gold (Invitrogen, P36930) mounting medium [40]. All the slides were imaged using a Zeiss fluorescence microscope (Zeiss Axio Imager 2).

Section pictures were analyzed using ImageJ2 software (version 2.9). Each intact muscle fiber contour was drawn using laminin markings to calculate muscle fiber size. The reliable minimal Feret's diameter (MFD) indicator of muscle fiber size was used. With this indicator, the smallest diameter of the muscle fiber is minimally influenced by oblique sectioning of the muscle and therefore less prone to measurement errors than the cross-sectional area [41]. 3MHC staining was used to calculate the proportion of each myofiber type and classify MDF data into myofiber types. Each muscle section contained a minimum of one hundred muscle fibers and only the participants for which histomorphological data were available for the two-time points were included in the analysis.

2.6. Data analysis

Descriptive statistics for age, CTGn repeats, training attendance, and percentage of predicted strength of the four lower limb muscle groups were performed to provide an overview of the cohort. The percentage of predicted strength of each muscle group was calculated using the regression equations developed by Hogrel et al. [42]. All data were analyzed with bootstrap ($n = 1000$) nparLD nonparametric repeated ANOVA and posthoc nparLD subset tests limited to two measurement time points (R version 4.2.2 nparLD version 2.2). The comparisons of the five measurement time points were T0 vs. T1 (short-term effect of the training program), T0 vs. T2 (total effect of the training program), T1 vs. T2 (mid-term effect of the training program), T2 vs. T3 (short-term maintenance of the training program) and T2 vs. T4 (mid-term maintenance of the training program). Statistical significance was set at $p < 0.05$. For clinical measurements, individual difference between T2 and T0 performance was calculated for each outcome measure and analyzed using the standard error of measurement (SEM). When ICC was available for the DM1 population, the SEM was calculated using the standard deviation (SD) of our cohort at T0 as follows: $SDT0^{*}\sqrt{(1 - ICC)}$. The following SEM values were used for the analysis: TUG (0.9) [30], 30 s STS (0.6) [27] and 10mWT (0.03 for comfortable speed and 0.04 for maximal speed) [27]. For muscle biopsy analyses, descriptive statistics were done and inferential statistics using Wilcoxon tests. According to other exploratory studies, statistical significance was set at a p-value <0.1 for this specific set of analyses, considering the low number of available samples [43–45]. Data were analyzed using IBM SPSS Statistics for Mac version 28.0 (Armonk, NY: IBM Corp) and R version 4.2.2. For the qualitative analysis, the physical therapist (LGC) listened to the recording [46] and did a content analysis following the acceptability framework [39].

3. Results

3.1. Participants

Twelve women with DM1 were recruited. Eleven women completed the training program, with an average training attendance rate of 98.5 %. One participant had to be excluded due to medical reasons, despite completing six weeks of the training program including evaluations at T0 and T1. Muscle biopsy was not collected post-training for this participant. In addition, post-training muscle biopsies were not obtained from two other participants (one refused and only fat was collected for another one). Participant characteristics can be found in Table 1, including the mean and standard deviation of the cohort for each characteristic. The cohort had a mean age of 37.3 ± 10.5 years and an average of 490 ± 272 CTGn repeats. The cohort

Table 1
Participants' characteristics.

ID	Age (years)	CTGn repeats	Phenotype	Training attendance rate (%)	T3 follow-up attendance	T4 follow-up attendance	Muscle biopsy done	Percentage of predicted strength at T0 (%)			
								Knee extensors	Knee flexors	Hip extensors	Hip flexors
623	55	230	Late	100.0	Yes	Yes	T0	55.48	117.92	120.01	112.78
673	52	509	Juvenile	100.0	Yes	Yes	T0, T2	55.91	60.59	95.17	66.93
1751	33	462	Juvenile	95.8	Yes	Yes	T0, T2	73.34	75.35	61.50	78.73
1948	33	832	Juvenile	95.8	Yes	Yes	T0, T2	37.84	117.35	124.99	107.22
1973	39	70	Late	95.8	Yes	Yes	T0, T2	104.60	132.29	144.22	129.39
1996	36	694	Juvenile	NA	No	No	T0	66.31	70.11	83.41	69.50
2074	30	891	Juvenile	100.0	Yes	Yes	T0	41.42	37.97	61.86	63.35
2118	52	466	Adult	95.8	Yes	Yes	T0, T2	70.04	133.96	109.37	86.20
2134	24	488	Juvenile	100.0	Yes	No	T0, T2	65.06	81.46	91.76	91.66
2338	38	432	Adult	100.0	Yes	No	T0, T2	58.54	113.65	67.54	80.10
2351	25	300	Juvenile	100.0	No	No	T0, T2	70.05	109.52	145.26	97.29
2361	30	324	Adult	100.0	Yes	Yes	T0, T2	88.38	86.53	84.13	76.34
Mean	37.3	490	–	98.5	–	–	–	65.58	94.73	99.10	88.29
(SD)	(10.5)	(272)		(2.1)				(18.44)	(30.43)	(29.71)	(20.17)

SD: standard deviation. NA: not applicable.

exhibited different phenotypes as shown in Table 1. For the follow-up evaluations, 10 participants attended the three-month follow-up, and 8 participated in the six-month follow-up. All participants had a low percentage (65.58 %) of predicted strength for the knee extensors muscle group, except one participant. The percentage of predicted strength of knee flexors, hip extensors, and hip flexors varied between 88 and 99 %.

3.2. Clinical assessment

3.2.1. Muscle strength

There were significant training program-induced increases in the 1RM measurement for all exercises, see Fig. 2 (T0 vs. T2: $p < 0.001$). Interestingly, significant increases were reported in the two halves of the training program for all exercises (T0 vs. T1: $p < 0.001$ and T1 vs. T2: $p < 0.048$). At 3 months follow-up, 1RM squat strength significantly decreased (T2 vs T3: $p = 0.010$), but no change was measured at 6 months follow-up (180 ± 109 lbs at T2 vs. 185 ± 63 lbs at T4: $p = 0.664$), see Fig. 2a. The mean 1RM values for hip abduction, leg press, and leg extension at T3 and T4 were significantly lower compared to those measured at 12 weeks (Fig. 2).

The training also induced a significant increase in MIMS of the knee extensors (71 ± 31 Nm at T0 vs. 80 ± 34 Nm at T2: $p = 0.006$) with a significant gain in the first half of the training program (71 ± 31 Nm at T0 vs. 80 ± 31 Nm at T1: $p = 0.013$), see Fig. 3a. Increased MIMS did not show a lasting effect as strength decreased until reaching baseline values, at T3 and T4. MIMS of hip extensors also demonstrated a significant improvement induced by the training program (123 ± 52 Nm at T0 vs. 149 ± 56 Nm at T2: $p < 0.001$), followed by a significant decrease at T3 (101 ± 52 Nm) compared to the post-training value (149 ± 56 Nm; T2 vs. T3: $p < 0.001$), see Fig. 3c. Nevertheless, by the 9-month time-point (146 ± 59 Nm at T4), the mean strength had returned to a similar post-training value (T2 vs. T4; $p = 0.636$).

3.2.2. Functional tests

Participants did not demonstrate significant improvements in their functional mobility (as assessed by the TUG) and comfortable walking speed (as assessed by the 10mWT) following the completion of the training program, but showed a tendency of improvement for the 30 s STS (12.86 ± 2.93 repetitions at T0 vs. 13.91 ± 1.92 repetitions at T2; $p = 0.058$), Fig. 4. In addition, the change between T0 and T2 performance was beyond the SEM for the 30 s STS (see Table 2 for the difference in performance between T2 and T0 and Supplemental material 1 for raw data). In addition, there was a significant improvement in walking speed at the maximal pace between the baseline and 6-week assessments (1.58 ± 0.42 m/s at T0 vs. 1.68 ± 0.45 m/s at T1; $p < 0.010$), but no significant effect was measured at the end of the training program (T0 vs. T2). A tendency of improvement was observed for the ascent 10TST at a comfortable pace (6.28 ± 2.60 s at T0 vs. 6.19 ± 1.36 s at T2; $p = 0.059$). However, there was a significant reduction in comfortable ($p = 0.029$) and maximal ($p = 0.003$) speeds during stair descent assessed with the 10TST between the initial assessment (comfortable pace: 5.26 ± 2.25 s, maximal pace: 3.42 ± 1.06 s) and T2 (comfortable pace: 5.51 ± 1.72 s, maximal pace 4.37 ± 1.69 s).

Table 2
Change between T2 and T0 compared to the standard error of measurement (SEM).

Δ (T2-T0)	Mean change of the cohort	SEM of the cohort
TUG (s)	−0.28	0.92
30sSTS (rep.)	3.5*	0.59
10mWT confo (m/s)	0.015	0.027
10mWT max (m/s)	0.032	0.042

*Improvement outside the SEM. Legend: Δ = Change between T2 and T0.

3.2.3. Neuropsychiatric manifestation assessment

No significant changes were observed over time in the level of fatigue and somnolence as measured by the FDSS (Fig. 5a). Regarding apathy, the mean score of the AES-C was significantly decreased at 12 weeks in comparison to baseline (34.58 ± 8.34 at T0 vs. 31.18 ± 7.65 at T2; $p < 0.001$) and tends to keep decreasing up to month 6 (T2 vs. 28.60 ± 8.59 at T3; $p = 0.094$); interestingly, there is no significant increase in apathy scores in the late stage of the study (T2 vs 32.38 ± 7.52 at T4; $p = 0.414$), see Fig. 5b. Additionally, there was an improvement in the depression symptomatology, expressed by a significant decrease in the subscale of depression in HADS score between baseline and week 12 (3.75 ± 2.70 at T0 vs. 2.64 ± 1.36 at T2; $p = 0.021$).

3.2.4. Patient-reported outcomes and self-reported changes and perception

The LEFS score significantly improved between baseline and 12 weeks (64.58 ± 14.84 at T0 vs. 70.91 ± 11.26 at T2; $p = 0.003$) and demonstrated a lasting effect up to T4 (Fig. 6a). No significant changes were measured over time with the DM1-activ. At baseline, up to 83 % of the cohort experienced pain. Thus, pain score interference significantly improved after the training program,

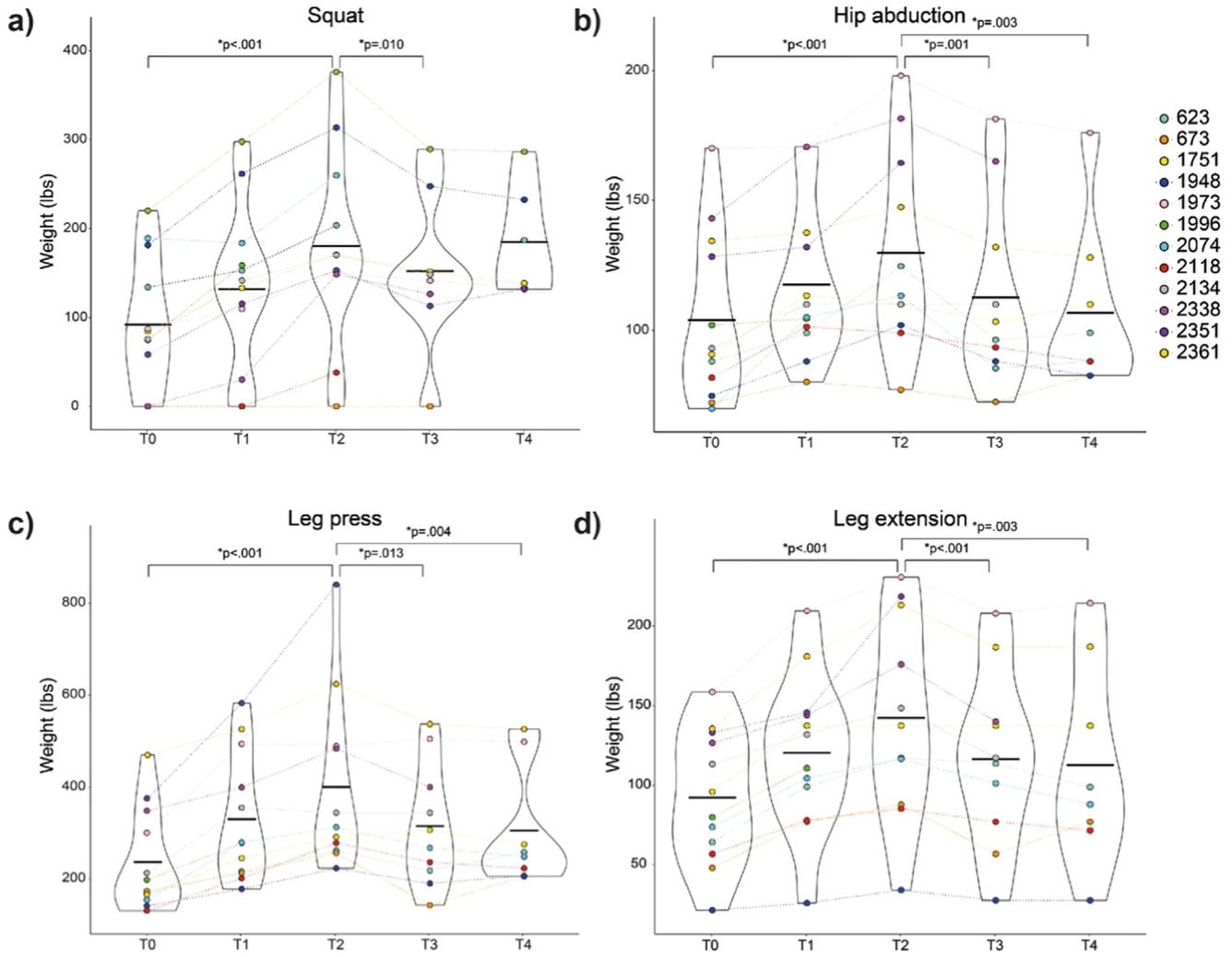

Fig. 2. Violin plots showing the distribution of 1-Repetition maximum (1RM) of all exercises of the program: a) squat, b) hip abduction, c) leg press, and d) leg extension. * means statistically significant ($p < 0.05$).

meaning that participants still had pain, but the pain interfered to a lesser extent in their daily activities ($p = 0.015$). This significant improvement was maintained up to 6 months after the end of the training program.

At baseline, only four participants reported falls and among them, only one had frequent falls occurring weekly (i.e. 30 falls in the last month and six falls in the last week). By the end of the training program, the number of falls for this participant decreased to two in the last month (Fig. 7) and none in the last week. However, at T3 and T4, the number of falls for this woman increased, with 10 falls in the last month and 3 to 4 falls in the last week.

Additionally, the level of physical activity was monitored at follow-up. Two participants out of ten were still doing personal strength training at T3 while this number reached three out of eight at T4 (Table 3).

Following the training program, participants reported numerous physical and neuropsychiatric benefits in their daily living, such as increased energy level ($n = 4$), better mood ($n = 3$), increased lower limb strength and endurance ($n = 8$), improvement in physical capacities related to mobility (climbing stairs, walking on inclined) ($n = 7$), improvement in balance ($n = 4$), and greater self-esteem ($n = 5$). In contrast, fatigue induced by the training has also been reported ($n = 3$). Furthermore, some barriers and facilitators to adherence have been identified by participants. The main facilitators were the supervision of training sessions, flexible schedules, being paired with other persons with the same disease, and affordability. The principal barrier was to include training sessions in their daily schedule. Overall, participants would recommend the training program to other persons having DM1.

3.3. Muscle biopsy analysis

For the 3MHC muscle fiber analysis, results from only eight participants were included. As reported in Table 1, muscle biopsies were collected in nine participants pre- and post-training, but the pre-training staining of participant #1751 was not valid due to technical error and consequently, this participant was not included in the analysis.

The cohort tends to have a higher proportion of type II muscle fibers than type I at baseline but no significant changes in the proportion of muscle fibers were observed between T0 and T2 (Table 4). Also, there was a significant increase of 9 % in the mean MFD of the muscle fibers overall after the training program ($p = 0.017$, Fig. 8). Significant increases in the mean MDF were also found after the training program for type I (Fig. 8 and Table 4).

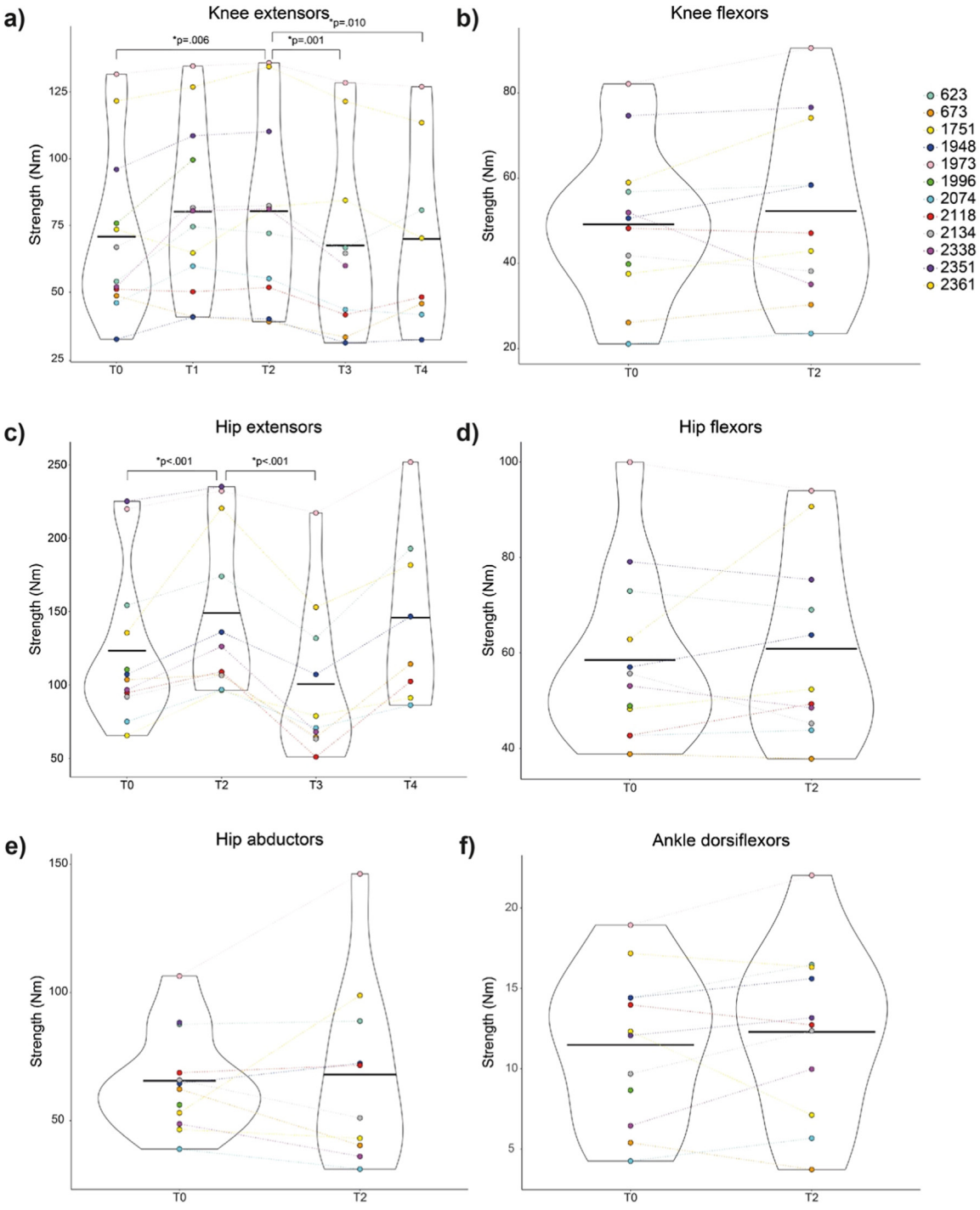

Fig. 3. Violin plots showing the distribution of maximal isometric muscle strength of the following lower limb muscle groups: a) knee extensors, b) knee flexors, c) hip extensors, d) hip flexors, e) hip abductors and f) ankle dorsiflexors. * means statistically significant ($p < 0.05$).

4. Discussion

This study focuses on the multisystemic impact of a 12-week lower-limb supervised resistance training program in a cohort of women with DM1. As this training program has been completed by eleven women, the results could be affected by the low number of participants and are therefore exploratory. We showed that resistance training had a significant positive impact on muscle strength and function, pain, as well as apathy and depression. Moreover, some of these gains were maintained up to 6 months after the end of the training program. Positive fundamental muscular adaptations to exercise were also seen following the training program. In addition, this study demonstrated that this training regimen was appreciated by our cohort of women with DM1. The persistence of many positive effects over 6 months after the end of the program suggests that, in a rehabilitation context, two blocks of 12-week therapy focusing on lower limb muscle strengthening could limit loss of muscle strength and function. This conclusion is consistent with that obtained in men with DM1 [14].

Considering ongoing drug developments in DM1 [47], exercise could be used as adjuvant to potentiate the pharmacological effect

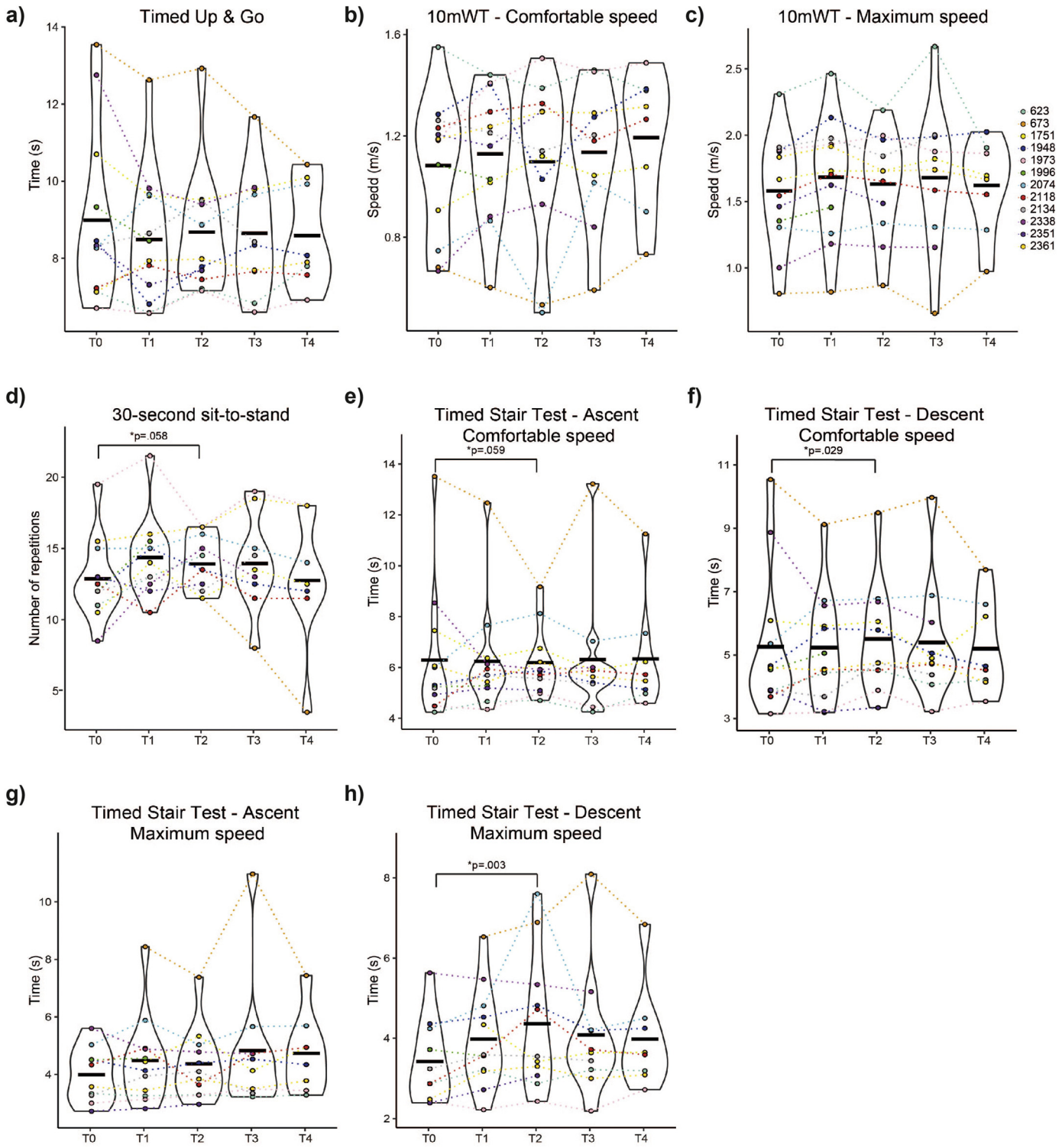

Fig. 4. Violin plots showing the distribution the following functional tests: a) Timed up and Go, b) 10 m Walk Test at comfortable speed, c) 10 m Walk Test at maximal speed, d) 30-second sit-to-stand, e) 10-step timed stair test – ascent at comfortable speed, f) 10 timed Stair Test – descend at comfortable speed, g) 10 timed Stair Test – ascent at maximum speed, h) 10 timed Stair Test – descent at maximal speed. * means statistically significant ($p < 0.05$).

as reported by Hu N. et al. 2021 in a mouse model of DM1 [48]. Also, as this program was tested on both men and women and assessed with multiple clinical and fundamental outcomes, the results obtained from this study will help to fill a gap in the literature and develop clinical guidelines aiming to reduce DM1 impairments [49]. Overall, women presented similar changes to those shown by men with DM1. Indeed, this type of training induced positive changes in both cohorts for MIMS of the knee extensors (13 % for women and 20 % for men), 1RM for all exercises (ranging from 25 to 95 % for women and 27–125 % for men), functional strength of lower limb (30sSTS; 8 % for women and 18 % for men) [14], perception of lower limb function

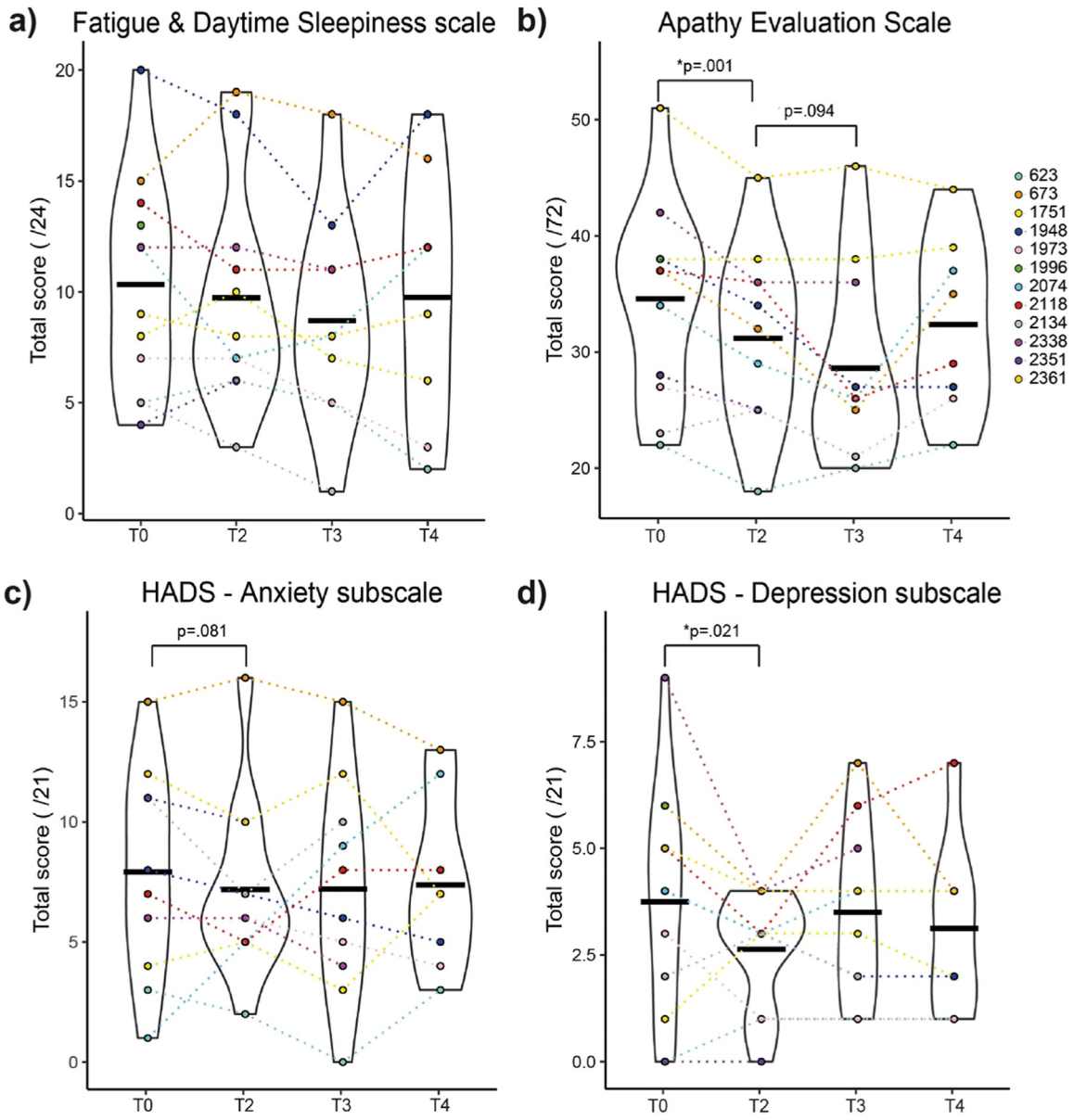

Fig. 5. Violin plots showing the distribution of the following neuropsychiatric assessments: a) Fatigue and daytime sleepiness scale, b) Apathy evaluation scale, c) Hospital anxiety and depression scale – anxiety subscale, d) Hospital anxiety and depression scale – depression subscale. * means statistically significant ($p < 0.05$).

(LEFS score), and apathy [15]. However, men also had benefits on walking speed and daytime sleepiness after the training program. Interestingly, even clinical manifestations that are less frequently reported for each sex at baseline according to Dogan et al. (2016), were improved by the training program (i.e. women increased muscle strength and men decreased somnolence).

As this program was designed to counteract lower limb muscle weakness, the assessment of muscle strength is the main outcome to consider in the interpretation of the results. The increases in MIMS of knee extensors and hip extensors were expected considering that these muscle groups were more targeted by the exercises of the program. A closer look at the results showed that the training program induced a more long-lasting effect on the MIMS of the hip extensors and the 1RM of squats, which were both maintained up to 6 months after the intervention. An explanation for this could be that squats were the most functional movement of the training program and the latter could have been executed more frequently in daily living once the program was over. In the same line of thought, hip extensors are a muscle group solicited in many daily tasks such as lifting weights and climbing stairs. The significant increase in the score obtained with the self-reported questionnaire used to assess the function of the lower limb [37] and its maintenance until month 9 supports this hypothesis. Our results also showed that the mean 1RM strength of squat and MIMS of hip extensors dropped at T3 compared to T2 but increased again at T4. One could speculate that at T4, more participants were doing lower limb strength training, but this number is quite low to impact the mean of the whole cohort (20 % at T3 vs. 37.5 % at T4) and it is worth noting that such training was unsupervised and likely sub-maximal. The loss of participants at follow-up could also have affected the results. Furthermore, for the exercise of squat, as explained in the method section, not all the participants could execute the exercise, then affected the number of participants included in the analysis. As muscle weakness is the main explanatory factor of disrupted social participation, these findings still support the additional importance

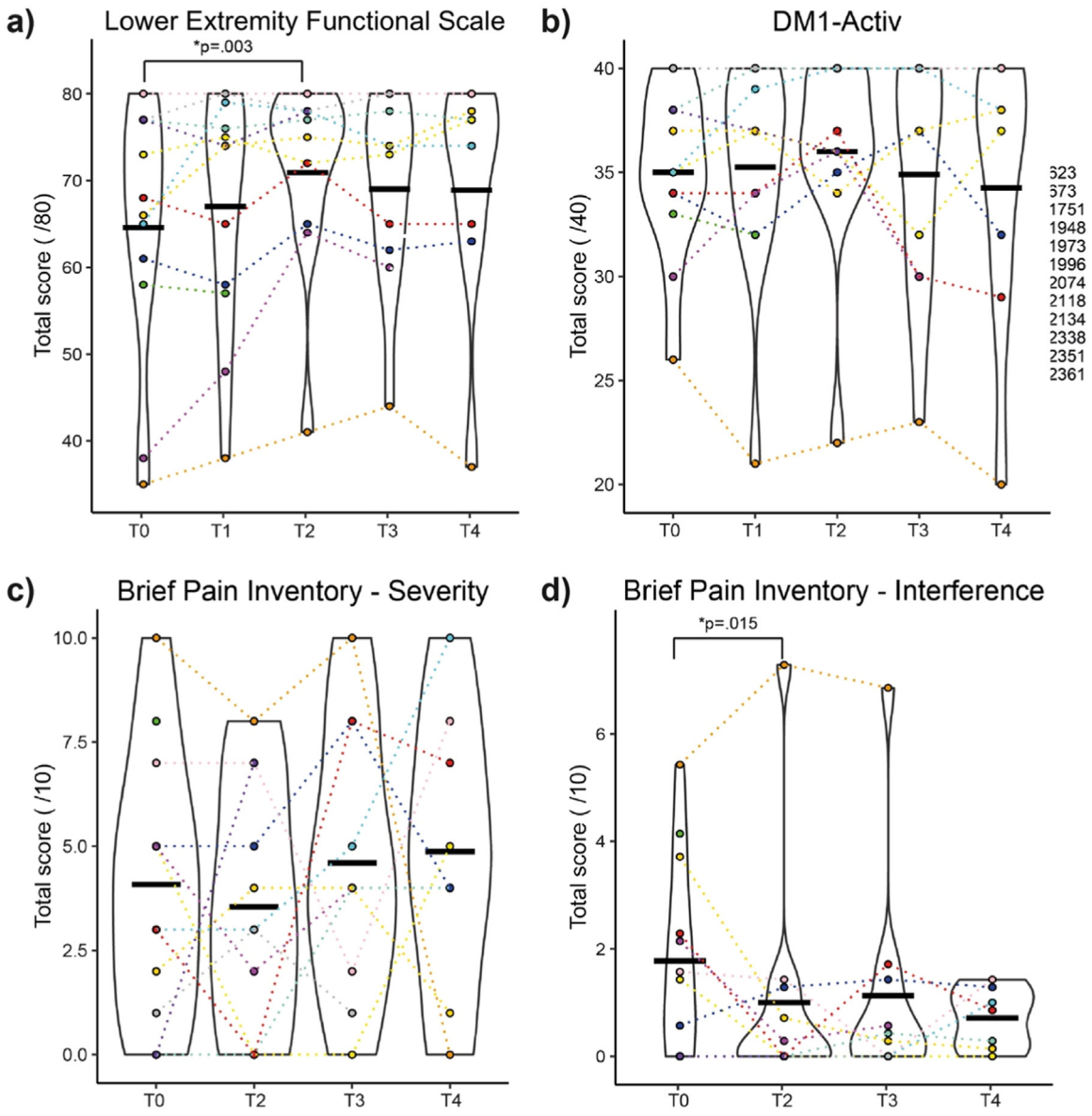

Fig. 6. Violin plots showing the distribution of the following patient-reported outcomes: a) Lower extremity functional scale, b) DM1-Activ, c) Brief pain inventory – Severity subscale, d) Brief pain inventory – Interference subscale. * means statistically significant ($p < 0.05$).

Table 3
Frequency and type of physical activity at follow-up.

	T3			T4		
	Did physical activity in the last month	Frequency	Type of physical activity	Did physical activity in the last month	Frequency	Type of physical activity
623	Yes	Twice a week	Salsa dance	Yes	Twice a week	Lower limb strengthening*
673	Yes	Once per day	Sit to stand: 3 series of 10 repetitions)*	No	NA	NA
1751	No	NA	NA	Yes	Two of three times a week	Upper and lower limb strengthening*
1948	No	NA	NA	No	NA	NA
1973	Yes	Once to twice a week	General strengthening*	Yes	Fourth times a week	General strengthening*
2074	Yes	Twice a week	Walks (30 min)	No	NA	NA
2118	No	NA	NA	No	NA	NA
2134	Yes	Twice a week	Hiking (2–3 h)	NA	NA	NA
2338	No	NA	NA	NA	NA	NA
2361	No	NA	NA	No	NA	NA

*Included in the count. NA: not applicable.

Table 4
Muscle biopsy analysis of proportion of fiber type and mean Minimal Feret's Diameter (MFD).

ID	Time	Proportions (%)		MFD (um)		
		Type I	Type II	Overall	Type I	Type II
673	T0	41.67	58.33	63.76	65.59	62.45
	T2	37.34	62.66	63.07	64.69	62.10
1948	T0	21.99	78.01	46.61	26.52	52.27
	T2	30.73	69.27	52.45	37.82	58.94
1973	T0	52.48	47.52	71.56	73.82	69.07
	T2	40.33	59.67	73.15	78.27	69.68
2118	T0	47.34	52.66	56.29	57.26	55.42
	T2	50.25	49.75	68.17	95.33	40.74
2134	T0	52.67	47.33	61.16	64.83	57.08
	T2	38.08	61.92	67.62	63.79	69.97
2338	T0	17.29	82.71	96.02	86.32	98.05
	T2	42.86	57.14	102.07	96.62	106.16
2351	T0	42.31	57.69	62.89	62.54	63.14
	T2	52.17	47.83	73.55	65.99	81.80
2361	T0	40.79	59.21	74.41	79.80	70.70
	T2	61.69	38.31	79.27	79.09	79.58
Mean (SD)	T0	39.57 (13.87)	60.43 (13.19)	66.59 (14.680)	64.58 (18.114)	66.02 (14.439)
	T2	44.18 (9.92)	55.82 (9.92)	72.42 (14.42)*	72.70 (19.13)*	71.12 (19.16)
p-values	–	NA	NA	$p = 0.017$	$p = 0.093$	$p = 0.208$

*Statistically different from T0 ($p \leq 0.01$).

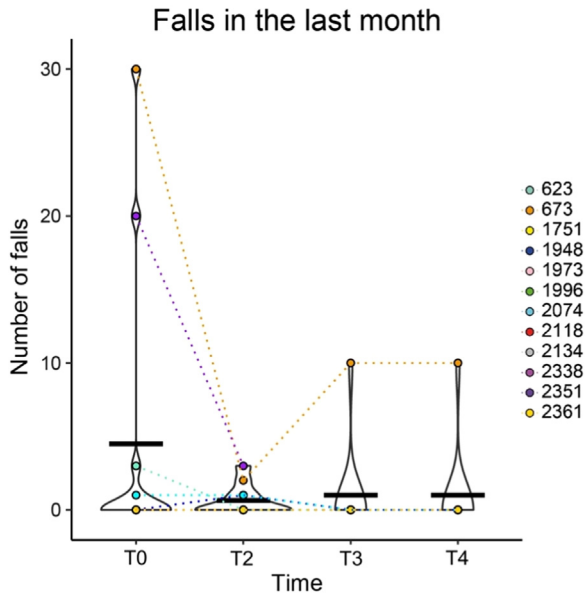

Fig. 7. Violin plots of falls reported by participants in the last month.

of strength training interventions in DM1 [9]. Also, the effects of resistance training in women with DM1 could be compared to strength training in non-affected older individuals. The Position Statement from the National Strength and Conditioning Association posits, for resistance training for non-affected older adults, an individualized, periodized approach with two or three training sessions per week, incorporating resistance exercises at intensities of 70 % to 85 % 1-RM [50]. Among the positive physiological adaptations to resistance exercise training of non-affected older adults, a 4–33 % increase in myofiber cross-sectional area was reported. Many factors including sex can explain this variability, with greater myofiber hypertrophy shown in older men. Then, the significant increase of 9 % in overall myofiber size seen in our cohort of women with DM1 after the training program is aligned with those conclusions. On the contrary, in the men cohort with DM1, evidence of muscle growth was only seen in a subgroup of participants showing abnormal values of hypertrophic factor at baseline [14]. Taken together our results showed that women with DM1 could potentially derive similar clinical and physiological benefits from this type of exercise regimen, helping to prevent loss of function in activities of daily living, as much as non-affected older individuals [51].

The intervention had a significant negative effect on the 10TST descending speed. Clinically speaking, the diminution of the speed at the 10TST could mean that our participants probably have a better technique for descending stairs and that it would be safer. We observed the same phenomenon in functional testing in adults with DM1, following a home-training program [52]. On the opposite, a tendency of improvement (beyond the SEM) was seen for the 30sSTS, in line with the improvement in lower limb strength previously discussed. Then, the mean TUG value of our cohort at baseline (see Supplemental material 1 for raw data) is comparable to the normative values of healthy women in their fifties [53], but it is still below the risk of fall cut-off [54]. Also, the walking speed at a comfortable pace (see Supplemental material 1 for raw data) is comparable to the normative values of healthy women in their fifties, while the maximal speed is comparable to the normative values of healthy women in their twenties [53]. High variability in our cohort could explain this, but apathy could also be a part of the explanation. Indeed, the lack of motivation in a submaximal test could affect the performance at normal speed in DM1. Thus, the 10mWT is a test known as reliable in DM1, but in that study of Knak 2020 [24], only the maximal speed in the 10mWT was measured.

This study showed that a 12-week strength training program has the potential to significantly reduce the apathetic symptomatology in women with DM1. Moreover, this significant effect lasts until 3 months after the end of the training, which is very encouraging because it means that "booster" sessions offered post-treatment (and before 3 months) may maintain the positive effect of the training program on apathy. This is in line with findings observed in men with DM1 participating in the same training program [15]. This means that the program, directly or indirectly, permitted to enhance participants' level of goal-directed activities, such as personal and instrumental activities of daily living (Behavior) as well as their goal-related thought content, i.e., interest, concern, or persistence (Cognition) [55]. These results are highly encouraging and in line with results observed in other conditions, such as dementia [56,57], where physical activity

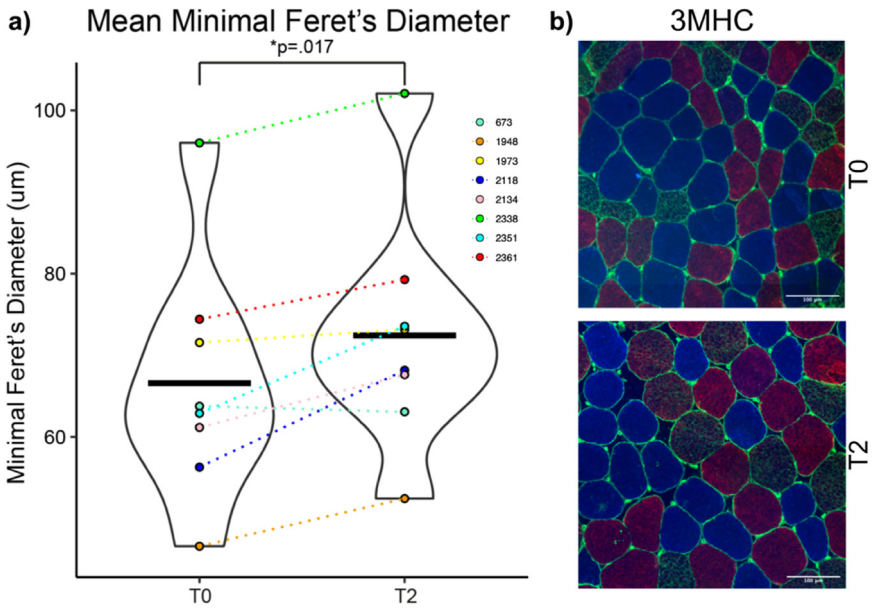

Fig. 8. Comparison of muscle biopsy pre- and post-training. a) Comparison of Mean Minimal Feret's Diameter b) 3MHC staining comparison of one participant between T0 and T2.

(including resistance training in a certain extent) is capable to diminish neuropsychiatric symptoms, including apathy among others (i.e., cognitive and mood disorders).

Contrastively to what was observed with men with DM1 [15], there was no treatment effect of the training program on fatigue/sleepiness in women. However, in detail, we observed a tendency to decrease in the FDSS score between baseline and month 6 which may correspond to the significant decline observed in men between baseline and month 9. Anyhow, one may retain that the training program did not produce any adverse effects on experienced fatigue or daytime sleepiness, despite the great physical efforts put in by the participants.

Regarding depression and anxiety, not only the training program did not produce adverse events, but rather diminished the level of symptomatology in participants' mood, especially during the program. As stated previously [15], this may be due to a secondary positive effect of the training program, where feeling stronger physically may reduce anxious preoccupations and depressive ruminations in participants. It is known that physical activity influences certain "biological and psychosocial processes also implicated in the pathophysiology of depression", namely neuroplasticity, inflammation, oxidative stress, self-esteem, social support, or self-efficacy [58,59]. Similar positive effects of training (including resistance training) on anxious or depressive symptoms were observed in healthy older adults with baseline low daily activity levels [60], as well as in patients with cognitive impairments [61].

If practicing physical activity may enhance mental health, it has been shown, even though scarcely, that ceasing activity may increase depressive symptoms [62]. However, since no significant difference was observed in the present study between the end of the program and the following data points (months 6 and 9), it is highly interesting to state that ending the program did not have a significant depressive-provoking effect. Thus, while there is little evidence to guide the non-pharmacological management of apathy in any condition and even less in DM1, this 12-week lower limb supervised resistance training program represents a promising avenue to overcome lack of motivation and diminished levels of activities frequently observed in DM1.

Many self-reported outcomes assessed in this study suggest that this training program benefits participants. Firstly, the prevalence of pain reported was in concordance with a previous study in DM1 showing a frequency of pain up to 83 % [6]. However, the level of pain interference decreased significantly after the training program, meaning that the pain was less limiting the daily lives of the participants. Secondly, the acceptability of the training program by all participants certainly had a positive impact on the adherence rate, as Sekhon et al. have already shown [39]. Lastly, participants reported many positive changes in their daily living, even though it was not reflected in the DM1-activ. The positive changes reported by the participants were both physical and neuropsychiatric. The neuropsychiatric changes could be induced by the physical activity, but also by the paired training and the supervision of the training session. As the present training program had several facilitators to ensure adherence to physical activity, it is remarkable that few participants decided to train by themselves outside the research setting after the end of the training program.

4.1. Strength and limitations

The main strengths of the study were the facilitators implemented to ensure a good attendance rate at the training sessions, such as a flexible schedule, calls and text message reminders to participants each Sunday, and paired and supervised training sessions. As these facilitators represented a good strength of the study, they also represented a limitation for replicability in the daily life of the population in DM1. Another strength is the assessment of muscle biopsy combined with strength, functional, neuropsychiatric symptoms, and self-reported outcomes, which give a complete portrait of DM1 and show the multisystemic impact of strength training in DM1. The number of participants also represents a limitation in this study along with the absence of a control group. Lastly, as participants with important health conditions leading to exercise restriction were excluded from this study, it remains unclear whether the intervention would be safe for those patients.

5. Conclusion & perspectives

This study provides additional findings to initiate the development of evidence-based guidelines for exercise prescriptions for people with DM1. In addition to gains observed in muscle function, a physical training program is a relevant therapeutic strategy to promote motivation, goal-directed activities, and mental health in this population. Also, the combination of the clinical and fundamental aspects could help to study the molecular mechanisms underlying the clinical improvements. Strength training is a beneficial therapeutic avenue for women with DM1 providing improvement to physical and neuropsychiatric impairments caused by the disease.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Laura Girard-Côté: Writing – review & editing, Writing – original draft, Resources, Project administration, Methodology, Investigation, Formal analysis. **Benjamin Gallais:** Writing – review & editing, Formal analysis, Conceptualization. **Cynthia Gagnon:** Writing – review & editing, Formal analysis, Conceptualization. **Marie-Pier Roussel:** Writing – review & editing, Formal analysis. **Marika Morin:** Writing – review & editing, Methodology. **Luc J. Hébert:** Writing – review & editing, Conceptualization. **Darren Monckton:** Formal analysis. **Jean-Philippe Leduc-Gaudet:** Writing – review & editing, Formal analysis. **Gilles Gouspillou:** Writing – review & editing, Formal analysis. **Vincent Marcangeli:** Writing – review & editing, Formal analysis. **Elise Duchesne:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.nmd.2024.05.009.

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