Multidimensional aspects of pain in myotonic dystrophies

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To analyze the frequency and intensity of pain and its association with different characteristics of patients with myotonic dystrophy type 1 (DM1) and type 2 (DM2), 52 adult genetically confirmed DM1 and 44 DM2 patients completed the Brief Pain Inventory questionnaire (BPI).

Frequency and average intensity of pain on numerical rating scale (0-10) were similar in DM1 and DM2 (88% vs. 86% and 4.6 ± 2.3 vs. 4.2 ± 1.8, respectively, p > 0.05). In DM1, average pain intensity showed strong association with longer duration of disease and inverse relation with cognition. In DM2, average pain intensity showed association with female gender and emotions. Average pain intensity correlated with Individualized Neuromuscular Quality of Life (INQoL) total score in both DM1 (rho = +0.30, p < 0.05) and DM2 patients (rho = +0.61, p < 0.01).

In conclusion, the majority of DM1 and DM2 patients have mild to moderate pain. Our results open new opportunities for behavioral and cognitive interventions.

Key words: myotonic dystrophy type 1, myotonic dystrophy type 2, pain, quality of life

Introduction

For many years inherited neuromuscular disorders were considered painless. In the last ten years plenty of evidence suggested that pain was very common and even one of the core features of certain diseases from this group (1-6).

Myotonic dystrophies are the most common inherited muscular disorders in adults (7). They are autosomal dominant diseases caused by pathological expansion of nucleotide repeats – CTG repeats in the DMPK gene in case of myotonic dystrophy type 1 (DM1), and CCTG repeats in the CNBP gene in case of myotonic dystrophy type 2 (DM2) (7).

Pain is present in about 50-80% of DM2 patients, being one of the main features of the disease with potential impact on quality of life (QoL) (8-10). In 11% of DM2 cases it may even be the first symptom of the disease (11). Pain is often overlooked in DM1 both by patients and physicians, who often have a greater focus on other symptoms, such as weakness, myotonia, heart problems and anesthesia risk. Such limited focus on pain may impact patient care, as other studies have reported high levels of pain in 45-77% of DM1 patients with its possible influence on QoL (1, 2, 4-6, 10, 12-14).

To the best of our knowledge, direct comparison of the pain features in patients with DM1 and DM2 has not been performed so far. Furthermore, myotonic dystrophies are multisystemic disorders affecting different organs including the central nervous system with different cognitive and behavioral impairments (7). These diseases also have an impact on social participation (15).

Previous studies usually assessed pain in DM1 patients together with patients with other neuromuscular disorders and investigated pain influence only on certain areas of life (1, 5). Number of pain studies in DM2 is even smaller giving only descriptive data of pain and its influence on QoL (9, 10, 16). Separate analysis of each type of DM and a comprehensive approach investigating different biological, behavioral, cognitive, and social aspects would define the most significant factors and help to eliminate confounding variables related to pain in these multisystemic diseases.

The aim of the study was to analyze frequency and
intensity of pain and its association with different characteristics of patients with DM1 and DM2.

**Patients and methods**

Approval for this cross sectional study was received from the Ethics Committee of the School of Medicine, University of Belgrade, and written informed consent was obtained from all subjects participating in the study. Adult DM1 (n = 52) and DM2 (n = 44) patients were consecutively recruited from the Inpatient Unit and Day Hospital of the Neurology Clinic, Clinical Centre of Serbia at the University of Belgrade from January 1, 2013 until September 30, 2014. Most of them were newly diagnosed, while others were hospitalized due to the regular check-ups but not because of the worsening of symptoms. Clinical and electrophysiological diagnosis was confirmed by Repeat Primed PCR and Southern blot analysis in DM1 and by Repeat Primed PCR in DM2 patients (17). Patients with congenital, childhood and juvenile form of DM1 were excluded from the study, as well as all DM1 and DM2 patients with other significant somatic, neurological and psychiatric disorders not related to the disease; in particular 3 patients with DM1 were excluded due to acute stroke, leg fracture and severe depression with suicide attempt respectively, and 4 patients with DM2 associated with other diseases (neuromyelitis optica, leg amputation in non-regulated diabetes, leukemia, and acute heart infarction).

Pain was investigated by the shorter version of the Brief Pain Inventory questionnaire (BPI) (18) since questions about pain interference were not analyzed in this study. Patients were asked if they, during the last four weeks (instead of the last 24 hours in the original questionnaire), had any pain or pain other than everyday kinds of pain seen even in healthy people from time to time. They were also asked to draw their sites with pain on body map, and to rate experienced pain on 0-10 numerical rating scale at its worst, least, and average in the last four weeks. They answered what pain medication they used and rated pain relief on 0-10 numerical scale.

Since the Muscular Impairment Rating Scale (MIRS) for severity of muscular involvement is applicable only in DM1 and not in DM2, manual muscle testing (0 to 5 scale according to Medical Research Council (MRC) scale) was performed by experienced neurologists (VRS, SP, DL, IB). We added strength of the weakest muscle of the proximal arms, distal arms, proximal legs and distal legs in both DM1 and DM2 patients, with maximum score being 20 (19). Duration of active hand grip myotonia and percussion myotonia of the thenar eminence was measured in seconds.

Patients completed the Individualized Neuromuscular Quality of Life questionnaire (INQoL) (20, 21). INQoL consists of 45 questions within 10 sections. Four sections measure the impact of common muscle disease symptoms (weakness, locking (aka myotonia), pain and fatigue). Five sections measure the influence of the muscle disease on particular areas of life (activities, independence, relationships, emotions and body image). The last section is related to disease treatment and it was not used in our study. Total INQoL score is calculated from five sections assessing the influence of the muscle disease on particular areas of life according to Vincent et al. (20). The final score for each of nine sections and total INQoL score is presented as a percentage of the maximum detrimental impact with a higher percentage indicating greater symptom impact or worse QoL.

Depressive symptoms were assessed with the Hamilton rating scale for depression (HamD) (22). Severity of fatigue was measured by the Krupp’s Fatigue Severity Scale (FSS) (23). The daytime sleepiness scale (DSS) was administered to all patients (24). In further text depression, fatigue and excessive daytime sleepiness were referred to as behavioral factors.

Educational level was measured as number of years spent at school. All patients underwent neuropsychological investigation performed by experienced neuropsychologists. Global cognitive status was assessed using the Mini Mental State Examination (MMSE) with score of ≤24 considered abnormal (25). No one of tested patients had MMSE ≤24, i.e. suspected dementia. For assessment of delayed verbal memory, the Rey Auditory Verbal Learning Test (RA VLT) was administered (26). Copy and recall of the Rey-Osterrieth Complex Figure (ROCF) was used to assess visuo-constructive abilities and visual memory (26). Speed and attention were assessed using the Trail Making Test A (TMT-A) (26). Executive functions were examined by the Trail Making Test B (TMT-B) (26). Tests were chosen in order to measure general cognitive level and major neuropsychological domains (visual ability, verbal and visual memory, attention and executive functions). All these tests have been widely used in patients with DM1 and DM2, including our cohorts (13, 19). Higher scores on MMSE, RA VLT and ROCF, and lower scores on TMT-A and TMT-B imply better cognitive achievement.

Normality of data was tested by the Kolmogorov-Smirnov test. For comparison between two groups χ² test, Mann-Whitney U test and Student t test were used, as appropriate. Correlations were calculated using nonparametric Spearman’s coefficient. Factors that significantly correlated with average pain intensity in the last four weeks were included in the first linear regression analyses. Four separate multivariate linear regression analyses were used for each group of independents (1. demographi-
ic and clinical, 2. behavioral, 3. cognitive, and 4. social). In this way, number of covariates in the final regression analysis was reduced. Final multivariate linear regression analysis encompassed all significant predictors from the first regression analysis to identify the factors with the strongest association with average pain intensity. At the both levels of regression analysis stepwise method was used – we entered all the univariately significant effects and SPSS made stepwise inclusion to fit the best model with the probability of $F$ to enter $\leq 0.05$ and to remove $\geq 0.10$. Using two levels of linear regression analysis all confounding variables and false positive findings were excluded. In all statistical analyses, significant testing was two-sided, with alpha set at 0.05 for statistical significance and 0.01 for high statistical significance.

**Results**

Frequency of any pain was similar in DM1 and DM2 (88.5% vs. 86.4%, $p > 0.05$) (Table 1). Frequency of pain other than everyday kinds of pain was even somewhat higher in DM1 patients but without statistical significance. The investigated demographic and clinical factors are presented in Table 2. Average pain intensity showed strong association with longer duration of disease in DM1 ($\beta = +0.47, p < 0.01$), and with female gender ($\beta = +0.38, p < 0.01$) and more severe muscular weakness in DM2 ($\beta = +0.58, p < 0.01$).

In patients with DM1, a strong association between average pain intensity and severity of fatigue was observed ($\beta = +0.41, p < 0.01$) (Table 2). In DM2 patients pain was related with the emotions subscale of INQoL ($\beta = +0.62, p < 0.01$).

The achievements on neuropsychological tests are presented in Table 3. In patients with DM1 the average pain intensity was inversely associated with results on MMSE ($\beta = -0.46, p < 0.05$), while in DM2 patients the strongest positive association was observed between pain and results on TMT-A ($\beta = +0.53, p < 0.01$).

The social characteristics of patients are given in Table 3. Pain intensity in DM1 subjects was in association with subdomain independence from INQoL ($\beta = +0.41, p < 0.01$), while in DM2 patients pain was related with INQoL subdomains independence ($\beta = +0.37, p < 0.05$) and relationships ($\beta = +0.35, p < 0.05$).

The results of the second multivariate linear regression analysis are presented in Table 4. The most significant factors related to pain in DM1 were duration of disease ($\beta = +0.35, p < 0.05$) and MMSE ($\beta = -0.46, p < 0.05$), while in DM2 patients pain was related with INQoL subdomains independence ($\beta = +0.37, p < 0.05$) and relationships ($\beta = +0.35, p < 0.05$).

Mean INQoL total score was similar in both patients groups (34.2 ± 28.9 in DM1 vs. 41.6 ± 23.7 in DM2, $p > 0.05$). Average pain intensity correlated with INQoL total score in both DM1 ($\rho = +0.30, p < 0.05$) and DM2 patients ($\rho = +0.61, p < 0.01$).

**Discussion**

Pain was present in almost 90% of DM1 and DM2 patients in the last four weeks prior to testing. Pain other than everyday kinds of pain was reported by 52% of DM1 and 39% of DM2 patients. In previous studies pain was found in approximately 50-80% of both DM1 and DM2 patients.

### Table 1. Frequency, sites and intensity of pain in patients with DM1 and DM2.

| Feature                  | DM1 (n = 52) | DM2 (n = 44) |
|--------------------------|--------------|--------------|
| Frequency of pain         |              |              |
| Usual pain (%)           | 88.5         | 86.4         |
| Unusual pain (%)         | 51.9         | 38.6         |
| Pain sites               |              |              |
| Head *                   | 7.7          | 25.0         |
| Neck                     | 3.8          | 0.0          |
| Shoulders                | 17.3         | 15.9         |
| Upper arms *             | 7.4          | 22.7         |
| Lower arms               | 9.6          | 15.9         |
| Hands                    | 11.5         | 13.6         |
| Trunk                    | 3.8          | 4.5          |
| Lumbosacral spine *      | 42.3         | 22.7         |
| Upper legs *             | 13.5         | 29.5         |
| Knees                    | 17.3         | 15.9         |
| Lower legs               | 34.6         | 40.9         |
| Feet                     | 7.7          | 11.4         |
| Number of pain sites     | 1.9 ± 2.0    | 2.2 ± 1.6    |
| Pain intensity †          |              |              |
| Minimum                  | 4.3 ± 2.6    | 3.6 ± 2.0    |
| Average                  | 4.6 ± 2.3    | 4.2 ± 1.8    |
| Maximum                  | 5.6 ± 2.6    | 4.9 ± 2.5    |
| Analgesics               |              |              |
| Use (%)                  | 46.2         | 47.7         |
| Pain reduction (%)       | 63.4 ± 38.0  | 64.6 ± 34.0  |

* p < 0.05 for comparison between DM1 and DM2 patients; † measured with numeric rating scale (0-10)
However, it is traditionally reported that pain is more common in DM2 than in DM1 (7, 8, 11). This may be due to the fact that DM2 is less severe in terms of muscular and multisystemic affection (7), thus pain might be the foreground of the disease. One third of DM2 patients considered pain the most disabling feature of their disease (16), and it represents the first symptom in 11% of patients (11). In line with this, in 3% of patients primarily diagnosed with fibromyalgia, a final diagnosis of DM2 was established (27). Similar or even higher percentage of pain in DM1 compared to DM2 patients found in our study should alarm clinicians to think about pain management in DM1, not only in DM2.

The most common sites of pain were lumbosacral spine and lower legs in DM1 patients, and whole legs in DM2. In both types of the disease pain was mostly located in the areas associated with locomotion which might have significant association with patients’ walking ability. Findings in previous studies were similar regarding the common involvement of different parts of legs (6, 7, 9, 16). Furthermore, leg pain had the highest contribution to the pain interference in DM1 (28). Lumbosacral pain was frequent in both DM1 and DM2 subjects, but more common in DM1. In previous studies, up to two third of DM1 patients had back pain (4, 6). Back pain in neuromuscular disorders including myotonic dystrophy, might be associ-

Table 2. Association of average pain intensity with demographic, clinical and behavioral factors in patients with DM1 and DM2.

| Feature                      | DM1 | Univariate analysis (p) | Multivariate analysis (beta, p) | DM2 | Univariate analysis (p) | Multivariate analysis (beta, p) |
|------------------------------|-----|-------------------------|--------------------------------|-----|-------------------------|--------------------------------|
| Demographic and clinical     |     |                         |                                |     |                         |                                |
| Females %                    | 55.8| 0.162                   | n.i.                           | 68.2| 0.016                   | +0.38, 0.002                  |
| Age at onset ** years, mean ± SD | 25.3 ± 8.6 | 0.337 | n.i. | 37.4 ± 12.0 | 0.882 | n.i. |
| Duration ** mean ± SD        | 19.9 ± 9.7 | 0.001 | +0.47, 0.001 | 16.0 ± 13.4 | 0.017 | +0.08, 0.548 |
| Age ** years, mean ± SD      | 45.0 ± 10.7 | 0.194 | n.i. | 53.4 ± 11.1 | 0.006 | +0.03, 0.847 |
| MRC score ** mean ± SD       | 16.1 ± 2.6 | 0.017 | -0.17, 0.389 | 17.0 ± 2.3 | 0.002 | -0.12, 0.409 |
| INQoL weakness ** mean ± SD  | 48.9 ± 36.8 | 0.049 | +0.20, 0.129 | 60.6 ± 32.5 | 0.000 | +0.58, 0.000 |
| INQoL locking ** mean ± SD   | 44.1 ± 37.9 | 0.107 | n.i. | 42.3 ± 34.4 | 0.013 | +0.18, 0.199 |
| Active myotonia ** s, mean ± SD | 5.9 ± 2.4 | 0.697 | n.i. | 1.8 ± 1.9 | 0.686 | n.i. |
| Percussion myotonia ** s, mean ± SD | 8.8 ± 2.4 | 0.282 | n.i. | 3.7 ± 7.9 | 0.408 | n.i. |
| R² adjusted                  | 0.20 |                        |                                | 0.44 |                        |                                |
| Behavioral                   |     |                         |                                |     |                         |                                |
| HamD score ** mean ± SD      | 13.3 ± 8.0 | 0.022 | -0.01, 0.943 | 7.8 ± 8.0 | 0.001 | +0.17, 0.211 |
| INQoL emotions mean ± SD     | 29.2 ± 30.2 | 0.057 | n.i. | 32.3 ± 25.2 | 0.000 | +0.62, 0.000 |
| DSS mean ± SD                | 5.8 ± 2.9 | 0.076 | n.i. | 5.1 ± 2.8 | 0.462 | n.i. |
| FSS mean ± SD                | 35.2 ± 13.0 | 0.003 | +0.41, 0.003 | 38.2 ± 15.5 | 0.000 | +0.32, 0.064 |
| INQoL fatigue mean ± SD      | 41.9 ± 39.1 | 0.020 | +0.18, 0.221 | 54.3 ± 33.8 | 0.000 | +0.19, 0.305 |
| R² adjusted                  | 0.15 |                        |                                | 0.37 |                        |                                |

** p<0.01 when compared patients with DM1 and DM2; n.s. non-significant; n.i. not included in the multivariate analysis since it was non-significant in univariate analysis.
ated with weakness of specific muscle groups. The activation of the stronger muscles is increased in order to oppose the forces acting on joints and this might cause pain and even skeletal abnormalities, including painful spinal deformities. In addition to the musculoskeletal pain, it is of mention that headache was more common in our DM2 subjects with frequency of 25% as previously reported, and as similar as in general population (9). On the other hand, significant correlation between headache and QoL was reported in DM1 patients (28). Thus, there future studies regarding different aspects of headache, and not only musculoskeletal pain, are necessary in myotonic dystrophies and other neuromuscular disorders.

Patients with myotonic dystrophies in this series had mild to moderate pain without significant differences between minimum and maximum pain intensity. Similar pain intensity was found in previous studies (1, 7, 9, 10). Pain intensity is equal in DM1, DM2 and other muscular dystrophies, and as severe as in patients with low back pain and osteoarthritis (5). Frequency of patients not using analgesics was about 50%, which is in accordance with previous studies (4, 6, 9). This might be due to the fact that pain response to analgesics therapy is quite poor in myotonic dystrophies (16). In our patients and in previously investigated DM2 cohort, analgesics reduced pain in about 65% of cases (7, 9). It is of mention that our

Table 3. Association of average pain intensity with cognitive and social factors in patients with DM1 and DM2.

| Feature                        | DM1       | Univariate analysis (p) | Multivariate analysis (beta, p) | DM2       | Univariate analysis (p) | Multivariate analysis (beta, p) |
|-------------------------------|-----------|-------------------------|--------------------------------|-----------|-------------------------|--------------------------------|
| Cognitive                     |           |                         |                                |           |                         |                                |
| Education years, mean ± SD    | 11.0 ± 2.7| 0.268                  | n.i.                           | 11.4 ± 3.2| 0.025                  | -0.12, 0.507                  |
| MMSE ** mean ± SD             | 26.0 ± 2.6| 0.041                  | -0.46, 0.016                  | 28.0 ± 2.4| 0.172                  | n.i.                           |
| ROCF copy mean ± SD           | 21.8 ± 8.2| 0.059                  | n.i.                           | 19.7 ± 7.7| 0.672                  | n.i.                           |
| ROCF recognition mean ± SD    | 12.6 ± 5.3| 0.306                  | n.i.                           | 12.0 ± 4.3| 0.977                  | n.i.                           |
| RAVLT recognition ** mean ± SD| 13.3 ± 5.4| 0.219                  | n.i.                           | 27.4 ± 5.7| 0.007                  | -0.25, 0.176                  |
| TMT-A mean ± SD               | 61.0 ± 28.6| 0.253                  | n.i.                           | 61.9 ± 38.2| 0.012                  | +0.53, 0.002                  |
| TMT-B mean ± SD               | 163.9 ± 61.7| 0.084                  | n.i.                           | 144.9 ± 78.8| 0.038                  | +0.00, 0.992                  |
| R² adjusted                   | 0.18      |                        |                                | 0.26      |                        |                                |
| Social                         |           |                         |                                |           |                         |                                |
| Marital status (%)            |           |                         |                                |           |                         |                                |
| live with partner              | 50.0      | 0.499                  | n.i.                           | 32.6      |                        |                                |
| live without partner           | 50.0      |                        |                                | 67.4      | 0.557                  | n.i.                           |
| Work (%) **                   |           |                         |                                |           |                         |                                |
| manual labour                  | 26.9      | 0.092                  | n.i.                           | 34.1      |                        |                                |
| intellectual                  | 26.9      |                        |                                | 18.2      |                        |                                |
| unemployed                    | 28.8      |                        |                                | 6.8       |                        |                                |
| retired                       | 17.3      |                        |                                | 38.6      | 0.583                  | n.i.                           |
| INQoL activities mean ± SD    | 34.8 ± 31.9| 0.091                  | n.i.                           | 49.9 ± 29.6| 0.001                  | -0.01, 0.965                  |
| INQoL relations mean ± SD     | 18.1 ± 24.9| 0.026                  | +0.13, 0.493                   | 22.0 ± 23.1| 0.000                  | +0.35, 0.021                  |
| INQoL independence mean ± SD  | 32.7 ± 36.0| 0.004                  | +0.41, 0.003                   | 38.4 ± 32.4| 0.000                  | +0.37, 0.017                  |
| INQoL body image mean ± SD    | 35.8 ± 28.3| 0.024                  | -0.11, 0.632                   | 34.4 ± 21.9| 0.000                  | +0.153, 0.459                 |
| R² adjusted                   | 0.15      |                        |                                | 0.37      |                        |                                |

** p < 0.01 when compared patients with DM1 and DM2; n.s. non-significant; n.i. not included in the multivariate analysis since it was non-significant in univariate analysis.
In this study we identified different parameters associated with pain in myotonic dystrophies, opening new opportunities for pain therapy in DM1 and DM2. Although we performed a comprehensive analysis of different factors, they described only 28% of pain severity in DM1 and 50% in DM2. Therefore further studies are requested to find other significant dimensions of pain in order to improve the pain management in these diseases.

In DM1 the more severe pain was in strong association with a longer duration of disease and worse cognition measured with MMSE, in contrast with two previous papers that found no correlation between disease duration and pain severity in these patients. The authors hypothesize that patients in this study may have displayed adequate coping behavior to lessen pain severity (5, 6). However, patients with longer duration of DM1 had also lower quality of life (13, 29) which is in favor of inadequate coping mechanisms and maladjustments to the disease, probably due to the well-known brain impairment (30). In accordance with this, we found a strong correlation between pain severity and poorer achievement on MMSE. There is a possibility that subjects with cognitive impairment are not able to adequately process pain with impaired central nervous system. Also, Hosoi et al. (31) reported that patients with neuromuscular disorders sometimes are not able to express their emotional problems due to alexithymia, thus reporting more somatic complaints including pain. However, this relation might be bidirectional, i.e. pain might disturb patients during testing (6), though the latter is less possible since severity of pain was only mild to moderate. Our results suggest that cognitive behavioral therapy on people with DM1 might have positive impact on pain relief. One such multi-national trial named OPTIMISTIC is in progress in Europe (http://www.muscular-dystrophy.org/research/news/7711_optimistic_trial_for_myotonic_dystrophy_type_1_launches_in_newcastle).

In our DM2 cohort a strong association of pain severity with female gender and emotions was established. Female patients with neuromuscular disorders including DM1 reported more pain than males (1, 5). Since pain may be the first and the most disabling symptom of DM2, this might explain the fact that women usually predominate in series of DM2 patients. Depression is more common in DM2 patients with pain (7, 9). It is possible that DM2 patients are more depressed because of somatic pain, but also that pain is more commonly reported in patients with depression. Furthermore, patients with neuromuscular disorders and alexithymia probably report more pain (31). It seems possible that therapy for depression might also have positive impact on pain in DM2 patients. Although DM2 seems to be less severe disease than DM1, QoL is equally impaired in both diseases, which is in accordance with a previous study (10). In our study the severity of pain correlated with QoL in both types of myotonic dystrophy. Suokas et al (10) and Udd et al. (7) observed lower QoL in DM2 subjects with pain, and several previous studies reported correlations of pain and QoL in DM1 (5). Tieleman et al. (10) found association between pain and QoL only in DM2, not in DM1 subjects.

This study has a few limitations: 1. Though myotonic dystrophies are rare diseases, to make stronger conclusions a larger number of patients should be necessary; 2. the lack of a control group from general population not permitting us to compare pain intensity and to conclude what pain features are disease-specific, and 3. the cross

| Feature            | DM1 (beta, p) | DM2 (beta, p) |
|--------------------|--------------|--------------|
| Female gender      | n.i.         | +0.37, 0.005 |
| Duration           | +0.35, 0.047 | n.i.         |
| INQoL weakness     | n.i.         | +0.30, 0.060 |
| INQoL emotions     | n.i.         | +0.64, 0.000 |
| FSS                | 0.23, 0.203  | n.i.         |
| MMSE               | -0.46, 0.011 | n.i.         |
| TMT-A              | n.i.         | +0.22, 0.093 |
| INQoL relationships| n.i.         | -0.04, 0.875 |
| INQoL independence | +0.15, 0.384 | +0.07, 0.665 |
| R² adjusted        | 0.28         | 0.48         |

n.s. non-significant; n.i. not included in the second multivariate analysis since it was non-significant in the first multivariate analysis
sectional design. Follow-up studies are needed to resolve exact direction of observed correlations.

**Conclusions**

The majority of DM1 and DM2 patients have mild to moderate pain. These results open new opportunities for behavioral and cognitive interventions.

**Acknowledgements**

This study was supported by the Ministry of Education, Science and Technological Development of the Republic of Serbia – Grants #175083, #173016.

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