Journal of Pain Research

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ORIGINAL RESEARCH

The impact of changes in serum levels of metalloproteinase-2 and metalloproteinase-9 on pain perception in patients with disc herniation before and after surgery

This article was published in the following Dove Press journal:
Journal of Pain Research

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Purpose: The aim of our research was to investigate the link between serum levels of metalloproteinase-2 (MMP-2) and MMP-9, and the degree of pain experienced before and 1 and 3 months after microdiscectomy in 70 patients with disc herniation (DH).

Patients and methods: The control group (group C) consisted of 70 healthy subjects and the DH group consisted of 70 patients with sciatica pain caused by lumbar DH. Before (DH0) and 1 and 3 months after surgery, the patients were assessed in terms of the following biochemical parameters: MMP-2, tissue inhibitors of metalloproteinases-2 (TIMP-2), MMP-2/TIMP-2, MMP-9, TIMP-1, and MMP-9/TIMP1, and the following clinical parameters: Numeric Rating Scale for the back (NRS-B) and the leg (NRS-L) and the Pain Rating Index (PRI) and Present Pain Intensity (PPI) of the McGill Pain Questionnaire.

Results: No statistically significant correlations were observed following the biochemical and clinical assessments performed in group C and the DH group before surgery. After surgery (1 month), higher levels of TIMP-1 correlated with higher levels of NRS-B (rs =0.27; $p<0.05$). At 3 months after surgery higher levels of TIMP-2 and lower levels of MMP-2/TIMP-2 were correlated with higher levels of NRS-L (rs =0.27, $p<0.05$ and rs =−0.31, $p<0.05$, respectively) and higher levels of TIMP-2 were correlated with higher PRI scores (rs =0.27; $p<0.005$) and PPI scores (rs =0.35; $p<0.01$).

Conclusion: The results showed that MMPs are involved in DH and play a significant role in the perception of pain after DH surgery. However, the value of MMPs as a potential therapeutic target in pain treatment should be considered cautiously.

Keywords: neuropathic pain, disc herniation, metalloproteinases, tissue inhibitors of metalloproteinases

Introduction

Numerous articles describing the significance of metalloproteinases (MMPs) during intervertebral disc degeneration and subsequent disc herniation (DH),[1] have been published during the last two decades. MMPs are a family of zinc-dependent endoproteases with multiple roles in tissue remodeling and degradation of a wide spectrum of both extracellular matrix (ECM) and nonmatrix proteins.[2,3] Currently, upwards of 20 MMPs have been reported in vertebrates that can be categorized through substrate specificity as collagenases, stromelysins, gelatinases, and membrane-type MMPs. A broad range of MMP substrates underlies the pivotal role of

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DovePress
http://doi.org/10.2147/JPR.S201199

MMPs during both routine physiological processes (such as bone remodeling and nerve growth) and pathological states (such as arthritis and atherosclerosis).[2] MMPs are regulated by specific inhibitors (tissue inhibitors of metalloproteinases or TIMPS), cytokines (interleukin-1), and growth factors. They are catabolic molecules involved in processes of degradation.[4] For example, MMP-1 decomposes collagens, MMP-2 decomposes gelatin and MMP-3 decomposes proteoglycan, laminin and fibronectin. MMP-2 has been shown to play a pivotal role in the pathophysiology of lumbar disc disease.[5] A correlation was found between increasing levels of MMP-2 and -9 and the severity of degenerative disc disease.[6] Herniated lumbar discs evoke a spontaneous increase in MMP levels.[7,8] Enhanced production of MMP-1 and MMP-3 might play an important role in the spontaneous regression of disc materials.[9]

Additionally, some studies performed in animals have shown that MMP-2 and MMP-9 activity can be observed in different phases of neuropathic pain (NP) development.[10–12] MMP-9 shows rapid and short upregulation (1–3 days) in primary sensory neurons in the area of the dorsal root ganglions (DRGs) after spinal nerve ligation in mice. MMP-2 activity is seen later but is maintained longer (9–21 days) in satellite cells of the DRGs and spinal astrocytes.[10]

The results of animal and human studies have shown the important role of MMPs in the development of disc degeneration and NP, which indicates that MMPs are a possible target for therapeutic interventions.[13] This is of particular interest because conventional treatments are disappointing in chronic low back pain management.

The aim of the current research was to observe MMP-2 and MMP-9 serum levels in patients with DH who qualified for surgery, before and after the procedure. The influence of MMP-2 and MMP-9 on the degree of experienced pain was evaluated. This research could help to establish the role of MMPs in this particular group of DH patients, and also provides new information in terms of their significance as a potential therapeutic target.

Material and methods

Patients

70 patients with sciatica pain caused by lumbar disc herniation were admitted to the Department of Neurosurgery of the Medical University of Lublin. They qualified for surgery (microdiscectomy) and were prospectively enrolled in the study. All patients received written and verbal information regarding the research procedures. Signed informed consent was obtained from all participating patients. The study protocol and informed consent forms were approved by the Ethics Committee of the Medical University of Lublin in Poland in accordance with binding legislation in this field. The study was conducted in accordance with the Declaration of Helsinki.

The inclusion criteria for microdiscectomy were as follows: 1. patients aged between 18 and 80 years, 2. a diagnosis of clinically symptomatic DH, 3. a confirmation of the clinical diagnosis through magnetic resonance imaging (MRI). The exclusion criteria were: 1. previous corticosteroid therapy in the 3 months preceding surgery, 2. the presence of previous spine surgery or spinal stenosis, 3. the co-existence of other medical conditions such as rheumatoid diseases, diabetes, cancer, and psychiatric diseases, a recent surgery for reasons other than DH, pregnancy, and alcohol or drug abuse.

A total of 70 patients participated in the current study of which 32 were female and 38 were male. The patients were aged between 18 and 76, with a mean age of 38.75 years (SD =12.03). The time of pain duration was between 1 month and 12 years before surgery, with an average time of 12.68 months (SD =22.36). A total of 19 patients presented with protrusion, 43 with extrusion and 2 with bulging of the DH (6 patients lacked radiological data). The degree of degeneration of the DH was assessed as IV in 30, III in 29, II in 4 and I in 1 subject(s), in accordance with Pfirmanns' scale.

The control group (group C) consisted of 70 healthy subjects (32 women and 38 men) with no clinical signs of DH, aged 18–76 (M =39.23; SD =11.8). The patients and controls did not differ significantly in their age ($z = -0.202$; $p > 0.05$). The characteristics of the patients and controls are shown in Table 1.

Neurosurgical procedure

All surgeries were performed by one surgeon who used a standard microdiscectomy method. The procedure was carried out under general anesthesia.

Clinical assessment

All 70 patients were assessed in accordance with the Numeric Rating Scale (NRS) for the back (NRS-B) and the leg (NRS-L) separately, the Pain Rating Index (PRI) and Present Pain Intensity (PPI) of the short form of the McGill Pain Questionnaire (SF-MPQ), the Oswestry Disability Index (ODI) and the Beck Depression Inventory. The subjects were evaluated 1 day before surgery (group DH0) and

Table 1 Characteristics of patients and controls

	Clinical Group n=70	Controls n=70	Clinical Group vs Controls *p*
Age (years)	38.75±12.03	39.23±11.09	0.840
Mean ± SD; range	18–76	18–76	
Gender	F – 32	F – 32	1.0
Female – F, Male – M	M – 38	M – 38	
Time of pain (months)	12.68±22.36	-	-
Mean ± SD; range	1–144		

subsequently 1 (group DH1) and 3 months (group DH3) following the procedure.

Biochemical assessment

Sample collection

Blood samples were collected from all 70 patients 1 day prior to surgery, and 1 and 3 months after the microdiscectomy procedure. A total of 5 mL of venous blood was drawn in the morning and immediately centrifuged at 4,000× g for 15 min. The serum samples were immediately frozen at −80 °C until analysis.

MMP-2 and MMP-9 assessment

MMP-2 and MMP-9 activities were determined through gelatin zymography based on the visualization of free-gelatin areas digested by MMP-2 and MMP-9. Briefly, serum samples were diluted 1:50 in redistilled water, and were mixed in a 1:4 proportion with sample buffer containing 10% sodium dodecyl sulfate (SDS). The enzymes were separated through polyacrylamide gel electrophoresis on a 10% gel with 0.05% gelatin type A from porcine skin (G2500) (Sigma–Aldrich, USA). After separation, the gels were washed for 1 h to remove the SDS. Gel incubation was carried out overnight at 37 °C in a buffer containing 1% Triton X-100 (pH 7.2). Gels were stained using 0.1% Coomassie Blue R-250 in 20% methanol and 10% acetic acid, and subsequently the stain was removed in 20% methanol and 10% acetic acid. MMP-2 and MMP-9 were detected as clear bands on a blue background. Enzymes were identified by comparing their localization with molecular mass standards (SM0441) (Fermentas Life Sciences, Germany), as well as with standards of both gelatinases (R&D Systems Inc., USA). Zymographic gels were scanned and quantified using ImageJ software (National Institute of Health, USA). The activities of MMP-2 and MMP-9 were expressed as the optical density of the substrate lysis zone.

TIMP assessment

The plasma concentration of TIMPs was determined using an immunoenzymatic method with a commercially available Human TIMP-1 Quantikine Enzyme-Linked Immunosorbent Assay (ELISA) Kit (R&D Systems Inc., USA) and a Human TIMP-2 Quantikine ELISA Kit (R&D Systems Inc., USA), used in accordance with the manufacturer's instructions. The concentrations are expressed in ng/mL for TIMPs.

Statistical analysis

Statistical analysis was performed using the IBM SPSS Statistics (Statistical Package for Social Sciences) software for Windows (Version 24.0, Predictive Solutions Sp.z o. o., Poland). The mean, standard deviation, and maximum and minimum values are provided for descriptive analysis. Before comparative analyses, all data sets were tested for normal distribution using the Shapiro–Wilk test. The distribution of variables significantly differed from a normal distribution, and therefore nonparametric tests were used in the analyses. Statistical differences between non-dependent groups were evaluated using the Mann–Whitney U-test. Friedman's rank test and Wilcoxon signed ranks test were used to compare the levels of MMPs and pain intensity before and after surgery. Significance values were adjusted using the Bonferroni correction for multiple tests. The association between the biochemical and clinical data was assessed using Spearman's correlation. The level of significance was $\alpha = 0.05$.

Results

Clinical assessment of patients before and after surgery

The intensity of pain rated using the NRS decreased in both the back and legs (NRS-B and NRS-L) at 1 month (NRS-B $p<0.001$, NRS-L $p<0.001$) and remained stable at 3 months following surgery (NRS-B $p>0.05$, NRS-L $p>0.05$). However, the PRI and PPI of SF-MPQ scores

changed. Patients reported a decrease in pain as described through PRI and PPI 1 month after surgery ($p<0.001$) and pain levels remained stable at 3 months ($p>0.05$). ODI scores had decreased at 1 month ($p<0.001$) and continued to decrease during the next 2 months ($p<0.001$). An improvement in mood, as assessed using Beck's scale was observed, but only at 3 months post-surgery ($p=0.016$).

Biochemical assessment of levels of MMP-2, TIMP-2, MMP-2/TIMP/2 before and after surgery

Levels of MMP-2 ($p<0.001$) and TIMP-2 ($p<00.1$), but not MMP-2 activity, measured as an MMP-2/TIMP-2 index, were significantly higher in group DH0 compared with group C. However, there was a significant decrease in the activity of MMP-2 at 1 month ($p=0.001$) and 3 months ($p=0.034$) after surgery. This was the result of a significant increase in the level of TIMP-2 at 1 ($p<0.001$) and 3 ($p=0.021$) months after surgery and no changes in the level of MMP-2. There were no significant differences between the measurements performed at 1 month compared with those performed at 3 months after surgery. The level and activity of MMP-2 was lower when the signs of DH had been present for longer. However, this correlation was weak (rs =−0.23, $p=0.053$ and rs =−0.26, $p=0.044$) and was observed only as a result of measurements performed at 3 months following surgery, not those performed before surgery (Table 2).

Correlation between MMP-2, TIMP-2, MMP-2/TIMP-2 and clinical assessment parameters (NRS-B, NRS-L PRI and PPI of SF-MPQ) before and after surgery

No statistically significant correlations were observed in the biochemical and clinical (NRS-B, NRS-B and PRI, PPI) assessments performed in group C and group DH0 before surgery. After surgery, correlations were observed only at 3 months. A higher level of TIMP-2 and a lower level of MMP-2/TIMP-2 were correlated with a higher level of NRS-L (rs =0.27, $p<0.05$ and rs =−0.31, $p<0.05$, respectively), and a higher level of TIMP-2 was correlated with a higher PRI score (rs =0.27, $p<0.005$) and PPI score (rs =0.35, $p<0.01$) (Table 3).

Biochemical assessment of levels of MMP-9, TIMP-1, and MMP-9/TIMP1 before and after surgery

The level of MMP-9 ($p<0.001$) and MMP-9 activity measured as an MMP-9/TIMP-1 index ($p<0.001$) were significantly lower in the DH0 group than in the control group, but the level of TIMP-1 was higher ($p<0.001$). The level of MMP-9 and its activity (MMP-9/TIMP-1) did not change at 1 month after surgery, but the level of TIMP-1 increased ($p<0.05$) and remained stable until 3 months. We did not observe a dependence of the level of MMP-9, TIMP-1, and MMP-9/TIMP-1 on the duration of the signs of DH (Table 4).

Correlations between MMP-9, TIMP-1, and MMP-9/TIMP-1 with clinical assessment scales (NRS-B, NRS-L PRI and PPI of SF-MPQ) before and after surgery

There was no significant relationship between the values of the biochemical and clinical (NRS-B, NRS-L and PRI, PPI) parameters before surgery. A weak correlation between TIMP-1 and NRS-B was observed 1 month after surgery (rs =0.27; $p<0.05$). A higher level of TIMP-1 correlated with a higher level of NRS- B (Table 5).

Discussion

The results of the current study show that MMP-2 and MMP-9 are involved during DH, which corroborates the results of previous studies.[4,5,14] DH accounts for 4% of the total cases of mechanical low back pain.[15] A total of 70% of lumbar DH patients recover from sciatica within 6 weeks of its onset. The DH resorption process was demonstrated using sequential MRI, and this resorption process may be the reason for the relatively good prognosis in cases of DH.[15]

The results of the current study suggest that MMP-2 is involved in ECM remodeling which limits the detrimental effect of DH. This phenomenon is reflected by a comparison of the activity of MMP-2 in the DH0 and control groups and in its further changes after microdiscectomy. The results also showed the crucial role of TIMP-2 in this process. MMP-2 levels, but not its activity (MMP-2/TIMP-2), are higher in the DH0 group than in the control group. This unchanged activity is maintained by an increase in TIMP-2 levels. However, this process, which results in disc resorption through the degradation of collagen,[2,5] is insufficient in DH and causes nerve root

Table 2 Biochemical assessment of levels of MMP-2, TIMP-2, MMP-2/TIMP/2 before and after operation (**A**), 1 month (**B**) and 3 months (**C**) after operation. Comparison of the levels of MMP-2, TIMP-2, MMP-2/TIMP/2 in the group of patients before operation with the control group is included

	Clinical Group before operation n=70	Clinical Group 1 month after	Clinical Group 3 month after	Controls n=70	Clinical Group vs Controls Mann-Whitney test z	p	Friedman's ANOVA	p	pairwise comparison p
	a	b	c	d		a-d			
MMP-2 Mean ± SD	5549.14±242.87	5982.89±2689.50	5924.92±2519.08	2465.39 ±567.05	−5.39	< 0.001	2.6	0.273	a-b 0.060 a-c 0.179 b-c 0.654
TIMP-2 (ng/ml) Mean ± SD	163.27±64.65	215.07±107.99	190.17±65.69	99.22 ±42.07	−3.52	< 0.001	13.34	0.001	a-b < 0.001 a-c 0.021 b-c 0.157
MMP-2/ TIPM-2 Mean ± SD	40.29±26.37	33.57±21.23	34.87±19.36	27.47±8.61	−1.169	0.169	10.50	0.005	a-b 0.001 a-c 0.034 b-c 0.289

compression which produces continuous pain and neurological deficits.

The activity of MMP-2 decreased 1 and 3 months after surgery. The surgical removal of the causal factor, a fragment of the herniated disc, affected TIMP-2 levels. Increases in TIMP-2 levels limit MMP-2 activity, which is not required in the changed, postoperative conditions. The results of the current study suggest that the role of TIMP-2 as a regulator of MMP-2 activity is crucial in DH patients. According to previously reported results, ECM remodeling by MMPs under the condition of pressure overload is largely mediated by TIMPs.[4] The TIMP family proteins are inhibitors of MMPs and include four members, namely TIMP-1, -2, -3, and -4. TIMP-2 is specifically responsible for the regulation of MMP-2 activity. Under normal conditions, TIMP-2 can activate pro-MMP-2 to MMP-2. However, when the amount of TIMP-2 is excessive, MMP-2 expression can then be repressed by TIMP-2.[16] Therefore, TIMP-2 exhibits dual functions as it has the ability to activate pro-MMP-2 and inhibit active MMP-2 at the same time. However, there is a lack of change in MMP-2 levels during the 3 months following surgery, suggesting an ongoing inflammatory process.

Our findings related to MMP-9 and TIMP-1 fluctuation are not consistent with the previous observations of Crean et al, which showed an increased level of MMP-9 in a group of patients with DH and scoliosis.[6] Haro et al observed the presence of extracellular matrix modifications in lumbar disks and found that increased expression of MMP-9 was correlated with an increase in TIMP-1 expression in an animal model.[13] Liou et al found that MMP-9 was constitutively expressed in neurons and microglial cells, and was immediately upregulated after nerve injury, and returned to baseline levels at day 3 in animal models.[17]

Discrepancies in findings might be caused by differences between results derived from animals and human subjects. Moreover, the group of subjects included in the current study was homogeneous and consisted of patients in whom conservative treatment had failed and who needed surgery.

Our research has shown distinctive changes in the concentration of TIMP-1. The TIMPs differ in their affinity for specific MMPs, and their interaction does not always lead to inhibition. This is exemplified by TIMP-1, which binds pro-MMP-9, thus protecting this protease from MMP-3 cleavage.[18] These findings can explain the

Table 3 Correlations of MMP-2, TIMP-2, MMP-2/TIMP-2,MMP-9, TIMP-1, MMP-9/TIMP-1 with the scales of clinical assessment 3 months after operation

	NRS-back r_s (p)	NRS-legs r_s (p)	PRI r_s (p)	PPI r_s (p)
MMP-2	−0.033 9 (0.785)	−0.155 (0.202)	0.113 (0.375)	0.017 (0.893)
TIMP-2	0.115 (0.370)	0.271* (0.031)	0.271* (0.038)	0.348** (0.007)
MMP-2/TIMP-2	−0.014 (0.916)	−0.309* (0.014)	−0.022 (0.871)	−0.149 (0.265)
MMP-9	0.056 (0.648)	0.055 (0.656)	0.112 (0.379)	0.111 (0.385)
TIMP-1	0.184 (0.150)	0.169 (0.186)	0.195 (0.140)	0.225 (0.089)
MMP-9/TIMP-1	0.049 (0.700)	−0.014 (0.915)	0.049 (0.715)	0.055 (0.681)

Note: *Significance at the level $p<0.05$. **Significance at the level $p<0.01$.
Abbreviations: NRS, numerical rating scale; PRI, pain rating index; PPI, present pain intensity.

downregulation of MMP-9 in the DH patients in our examined group. The downregulation of MMP-9 and its activity before surgery and for 3 months afterwards may suggest its role as a detrimental factor during disc degeneration and herniation, and the mechanisms which limited its activity were observed (the increase in the level of TIMP-1). Previously reported data demonstrated that the rare allele of MMP9, rs17576, was associated with poor back pain recovery during a 5-year observation.[3] However, the current results may also suggest that mechanisms in which MMP-9 is involved, such as reduced barrier disruption, neutrophil infiltration, NP and inflammatory pain, are insufficient in patients examined in the current study.[18] This concept is supported by the observation that MMP-9 levels and its activity are lower in DH patients before surgery, although MMP-2 levels are increased. The process of DH activates different factors which interact with each other. MMP-2 activity is coordinated not only by TIMP-2 but also by MMP-7, -14, -15, -16, -24, and -25 and MMP-2 itself coordinates the activity of MMP-9.-[2,14,20] The current results have shown the positive dependence between MMP-2 and MMP-9 in a group of patients with DH before surgery, and 1 and 3 months following surgery.

The role of MMPs in the perception of NP requires further investigation. Although we observed a decrease in pain intensity (as assessed through NRS-B, NRS-l and SF-MPQ) in DH patients after surgery, we did not find direct correlations between changes in levels of MMP-2 and MMP-9 and their activities or TIMP-2 and TIMP-1 levels. These findings, the lack of significant correlations between the measured biochemical substances and the results of the clinical assessment scales in the group of patients before surgery suggest that the pain which accompanies DH is a complex phenomenon in which many processes interact. Observations made in animal models of NP are valuable but are not reflected by the pain experienced by human subjects with DH. The pain, which is one of the symptoms of DH, has a different origin and clinical manifestation, and is considered to be a combination of neuropathic and nociceptive pain. The NP is a result of irritation of the nervous root by the herniated disc and is localized in the parallel dermatome. The nociceptive pain can be evoked by the stimulation of nociceptive receptors by the degenerated disc and arthritic changes in zygapophysial joints which accompany the herniated disc.[19] The diffuse pain localized to the lumbosacral region of the back is considered to be secondary to the forms of pain mentioned above. However, in the current study, a higher level of TIMP-2, and a lower level of MMP-2/TIMP-2 were correlated with a higher level of NRS-L, and a higher level of TIMP-2 was correlated with higher PRI and PPI scores at 3 months following surgery. This suggests the involvement of MMP-2 in the NP process, which could explain the relationship between the increase in the level of TIMP-2 in patients with higher scores in clinical scales characterizing NP, and also the weak correlation between TIMP-1 and NRS-B observed 1 month after surgery. A higher level of TIMP-1 was correlated with a higher level of NRS- B. This suggests that the involvement of MMP-9 in nociceptive pain can be increased through microdiscectomy.

Targeted therapy using specific MMP inhibitors in DH patients has been suggested by some authors.[20] Haro et al demonstrated that MMP-7 plays a crucial role in the DH resorption process. They suggested that recombinant human MMP-7 may be an ideal candidate for a chemonucleolysis drug.[13]

The effectiveness of such a treatment may be of limited value in treating the pain problems of DH patients. The results of the current study indicate that MMP-2 and MMP-9 can be involved in processes leading to both nociceptive and neuropathic pain but probably as single

Table 4 Biochemical assessment of levels of MMP-9, TIMP-1, MMP-9/TIMP1 before (**A**), 1 month (**B**) and 3 months (**C**) after operation. Comparison of the levels of MMP-9, TIMP-1, MMP-9/TIMP/1 in the group of patients before operation with the control group is included

	Clinical Group before operation n=70	Clinical Group 1 month after	Clinical Group 3 month after	Controls n=70	Clinical Group vs ControlsMann-Whitney test z	*p*	Friedman's ANOVA χ^2	*p*	pairwise comparison *p*
	a	b	c	d		a-d			
MMP-9 Mean ± SD	10618.23±4697.3	10618.23 ±4116.53	10700.45 ±4293.21	14553.23 ±2960.06	−3.59	< 0.001	0.371	0.831	a-b 0.621 a-c 0.804 b-c 0.826
TIMP-1 (ng/ml) Mean ± SD	381.65±152.36	420.04±123.34	432.77±208.95	157.41 ±108.97	−4.88	< 0.001	6.5	0.039	a-b <0.05 a-c 0.231 b-c 1.00
MMP-9/ TIMP-1 Mean ± SD	33.43±21.31	30.21±24.24	29.50±18.69	240.30 ±436.45	−5.22	<0.001	3.5	0.174	a-b 0.076 a-c 0.045* b-c 0.957

Note: *Significance at the level $p<0.05$.

Table 5 Correlations of MMP-2, TIMP-2, MMP-2/TIMP-2,MMP-9, TIMP-1, MMP-9/TIMP-1 with the scales of clinical assessment 1 month after operation

	NRS-back r_s (*p*)	NRS-legs r_s (*p*)	PRI r_s (*p*)	PPI r_s (*p*)
MMP-2	−0.078 (0.525)	−0.174 (0.154)	0.055 (0.666)	−0.092 (0.469)
TIMP-2	−0.128 (0.308)	−0.094 (0.454)	−0.049 (0.709)	−0.029 (0.828)
MMP-2/ TIMP-2	0.017 (0.891)	−0.052 (0.681)	0.049 (0.707)	−0.034 (0.798)
MMP-9	−0.018 (0.881)	−0.091 (0.455)	0.068 (0.589)	−0.005 (0.970)
TIMP-1	0.269* (0.032)	−0.038 (0.768)	0.212 (0.104)	0.149 (0.259)
MMP-9/ TIMP-1	−0.123 (0.333)	−0.010 (0.937)	−0.097 (0.459)	−0.097 (0.463)

Note: *Significance at the level $p<0.05$.

Abbreviations: NRS, numerical rating scale; PRI, pain rating index; PPI, present pain intensity.

elements of a complex chain of diverse and sometimes opposing processes. Therefore, the value of MMPs as a potential therapeutic target in pain treatment should be considered cautiously. MMPs are a heterogeneous group of enzymes which have low tissue specificity. A single enzyme may not represent a good biomarker of a mechanism in which it is involved.[21]

The biochemical processes which are observed during disc degeneration are very complex and are likely to be determined by a combination of factors, with gene-environment and gene-gene interactions that uniquely determine the progression of degeneration in each individual.[4,22]

Conclusion

The current study has shown that MMPs are involved in DH and can play a role in pain perception after DH surgery. However, the value of MMPs as a potential therapeutic target in pain treatment should be considered cautiously.

Disclosure

The authors report no conflicts of interest in this work.

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