Limitations of this study were as follows. The surgical technique was not identical among the patients because the surgeries were not performed by a single surgeon. Overall, 5 spine surgeons participated in this study. However, before starting the study, the procedures were standardized among the 5 surgeons to minimize the technical differences. Furthermore, the proportions of surgeries performed by each surgeon were almost identical between the 2 treatment groups. The other limitation was the withdrawal of the 7 patients (17%) from the study. The reasons for the withdrawal were the extension of decompression levels or the conversion of the procedure from decompression to fusion after randomization. However, we do not think that these withdrawals had a major impact on the results. Another limitation was that the measurements used in this study for evaluating the wound pain were not well validated except for the VAS. Because we believed that evaluation of the wound pain by only the VAS was insufficient, we added our nonvalidated original measurements to provide supplemental data, knowing that the measurements were less reliable. However, despite these limitations, we believe the results of the present study indicated that split laminectomy was less invasive, and reduced postoperative wound pain compared with conventional laminectomy.

Conclusions

The present prospective, randomized, controlled study confirmed that LSPSL for LCS reduces acute postoperative wound pain compared with conventional laminectomy, possibly because of minimized damage to the paraspinal muscles.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Matsumoto, Watanabe, Toyama, Chiba. Acquisition of data: Watanabe, Ikegami, Tsuji, Ishii, Ogawa, Takaishi, Nakamura. Analysis and interpretation of data: Watanabe, Nishiwaki. Drafting the article: Watanabe. Critically revising the article: Watanabe. Reviewed final version of the manuscript and approved it for submission: all authors. Statistical analysis: Ikegami, Nishiwaki. Study supervision: Matsumoto, Toyama, Chiba.

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Japanese Orthopaedic Association Back Pain Evaluation Questionnaire (JOABPEQ) : An Association Study in Patients with Lumbar Disc Herniation and Lumbar Spinal Canal Stenosis

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Key words : low back pain, lumbar disc herniation, lumbar spinal canal stenosis, questionnaire

Introduction

In 1997, the JOA revised the JOA score for low back pain and developed a new scientific outcome measure called JOABPEQ. The basic concept for developing JOABPEQ was to evaluate patients with low back pain from various specific perspectives, such as dysfunction, disability, handicap, and psychological problems. Furthermore, such measures should be patient-oriented, and its reliability and validity should be confirmed by statistical analysis. A paper has been published confirming the availability of JOABPEQ evaluating the short-term effects of surgical treatment for patients with lumbar disc herniation (LDH) or lumbar spinal stenosis (LSS)[5]. The aim of this study is to confirm the availability of JOABPEQ again using longer follow-up surveys.

Materials and Methods

1. Patients

Since April 2008, nineteen institutions were asked to recruit patients with LDH or LSS, who were admitted to their hospital for surgery, with the intention of collecting at least 200 patients with each disorder. Patients with typical LDH and LSS symptoms who underwent surgery at these institutions were included. Exclusion criteria were patients with previous surgery, other musculoskeletal disease requiring medical treatment, mobility aids or psychiatric disease that could potentially lead to inappropriate answers.

2. Applying the Questionnaire

The recruited patients were asked to complete the self-estimated questionnaire (JOABPEQ) and VAS scores (low back pain and leg pain) preoperatively, six and twelve months postoperatively. Additionally, patients were asked to judge the five self-rated

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Table 1 Comparison of the JOABPEQ scores in the LSS and LDH groups

		LBP	Lumbar ability	Walking ability	Social life ability	Mental health
LSS group	Pre-ope	43.0	58.0	21.0	36.5	48.5
	6 M	100**	83.0	79.0**	65.0	64.5
	12 M	100**	83.0	71.0**	65.0	66.0
LDH group	Pre-ope	29.0	50.0	29.0	32.0	46.5
	6 M	100**	100**	100**	78.0**	67.5
	12 M	100**	100**	100**	86.0**	59.0

Wilcoxon signed-ranks test **$p<0.01$

improvement grades regarding each of the five categories of JOABPEQ using a four-step rating scale (improved, slightly improved, no change and aggravated). The attending doctor was asked to record the JOA score, and the overall grades of improvement (improved, slightly improved, no change and aggravated).

3. Statistical Analysis

SPSS Statistics (Japanese version 17.0) was used to perform statistical analyse. Mann-Whitney's U test and t-test were used to evaluate the effect of surgical treatment demonstrated by JOABPEQ, JOA score and VAS. Spearman's rank correlation coefficient was calculated to determine the relationship between the total points of the JOA score and each factor of the JOABPEQ score, and the relationship between the changes of postoperative JOABPEQ scores and the grade of improvement assessed by patients or attending doctors. p values less than 0.05 were considered significant.

Results

In this study, three hundred and forty-three patients (LDH group : 75 patients, LSS group : 268 patients) were surveyed between April 2008 and February 2010. Mean patient ages in the LSS group and LDH group were 68.0 years and 46.0 years, respectively, showing a significant difference between the two groups.

1. JOA score

Mean JOA scores of the LSS group were 15.4, 22.8 and 23.0 points preoperatively, 6 and 12 months postoperatively, and mean JOA scores of the LDH group were 14.6, 25.3 and 25.8 preoperatively, 6 and 12 months postoperatively, respectively.

2. JOABPEQ

The median preoperative and postoperative JOABPEQ scores are shown in Table 1. In the LSS group good recovery was obtained only in two functional domains (low back pain and walking ability). In the LDH group, good recovery was obtained in four functional domains (low back pain, lumbar function, walking ability and social life function).

3. VAS

The average VAS scores for low back in LSS/LDH group was 5.7/4.7 preoperatively and 2.3/1.7 and 2.6/1.9 at 6 and 12 months postoperatively, respectively. The average VAS scores for leg pain was 6.3/6.4 preoperatively and 2.6/1.5 and 2.8/2.0 at each postoperative time point. Each score was apparently decreased after surgery in both groups.

4. The Correlation between JOA score and JOABPEQ

We assessed the correlation between JOA score and JOABPEQ preoperatively and postoperatively (Table 2). In the LSS group, there was a correlation between JOA score and each functional category of JOABPEQ both preoperatively and postoperatively. This suggest-

Table 2 The correlation between JOA score and JOABPEQ

		Preoperatively	After 6 months	After 12 months
LSS group	Low back pain	0.35**	0.42**	0.47**
	Lumbar function	0.45**	0.53**	0.56**
	Walking ability	0.34**	0.57**	0.74**
	Social life function	0.43**	0.57**	0.73**
	Mental health	0.31**	0.50**	0.61**
LDH group	Low back pain	0.42**	0.41**	0.24
	Lumbar function	0.45**	0.41**	0.54**
	Walking ability	0.46**	0.42**	0.42**
	Social life function	0.40**	0.42**	0.51**
	Mental health	0.33**	0.30*	0.24

*$p<0.05$, **$p<0.01$

Table 3 The correlation between JOABPEQ and self-assessments by doctors and patients

		Assessment by doctors		Assessment by patients	
		6 M ($n=210$)	12 M ($n=135$)	6 M ($n=235$)	12 M ($n=150$)
LSS group	Low back pain	0.27**	0.37**	0.33**	0.46**
	Lumbar function	0.20**	0.27**	0.24**	0.32**
	Walking ability	0.47**	0.50**	0.48**	0.61**
	Social life function	0.35**	0.45**	0.40**	0.48**
	Mental health	0.34**	0.33**	0.46**	0.40**
		6 M ($n=65$)	12 M ($n=36$)	6 M ($n=65$)	12 M ($n=36$)
LDH group	Low back pain	0.38**	0.26	0.36**	0.13
	Lumbar function	0.18	0.03	0.23	0.03
	Walking ability	0.26*	0.14	0.22	0.19
	Social life function	0.25*	0.38*	0.31*	0.45**
	Mental health	0.31**	0.39*	0.33**	0.26

*$p<0.05$, **$p<0.01$

ed that these measure would show a stronger correlation at a later postoperative time. In the LDH group, there was a correlation between the JOA score and every functional category of JOABPEQ except for the factor of low back pain and mental health 12 months preoperatively. And the tendency toward a stronger correlation at a later postoperative time was not recognized in this group.

5. Correlation between the Changes of Postoperative JOABPEQ scores and Assessments by Doctors and Patients

Table 3 shows the correlation between the postoperative changes in the points for each factor of JOABPEQ and changes in the grades assessed by attending doctors and patients themselves. In the LSS group, there was a significant correlation in every functional category. These findings suggested that JOABPEQ could properly reflect the assessments by attending doctors and patients themselves in the LSS group. In the LDH group, there were not as many correlations demonstrated between JOABPEQ and assessments by doctors or patients, and this showed a tendency toward fewer correlations 12 months postoperatively than there were 6 months postoperatively.

Discussion

The new outcome measure for low back pain, JOABPEQ published in April 2007, has gradually

become more widely used[6,7]. Its remarkable features are follows :

The First, JOABPEQ is a patient-oriented outcome measure that is preferable to exclude physician's bias, while the JOA score is a disease specific and physician-oriented outcome measure that mainly assesses the neurological status of the patient and enables surgeons to evaluate the results of surgical treatment. The Second, JOABPEQ includes 25 questions that are divided into five domains designated as : (1) low back pain, (2) lumbar function, (3) walking ability, (4) social life function and (5) mental health, making it a comprehensive outcome measure. The Third, JOABPEQ contains original equations that yield scores for the five factors. Then the equations to calculate the score for each domain are assembled in order to intuitively indicate the status of patients in five different functional domains.

The reliability and validity of JOABPEQ have been confirmed by statistical analysis[1~4]. Investigations have been performed in order to verify the sensitivity of the functional scores for treatment results in patients with low back pain, although another investigation is required to verify its sensitivity for each lumbar spinal disorder : such as lumbar disc hernia or lumbar spinal canal stenosis.

This study was performed to confirm the validity of JOABPEQ for evaluating the effects of surgical treatment in patients with LDH or LSCS, and the first report has been published evaluating the short-term results[5]. We reported results analyzing 6 and 12 months postoperative data from 343 patients (LSCS : 268 patients, LDH : 75 patients).

These results indicated that JOABPEQ is highly sensitive for assessing treatment results in both LSS and LDH patients. Furthermore, it was shown that there was a difference in the assessment of postoperative results between the LSS and LDH groups.

In the LSS group, there was a significant correlation between each functional category on JOABPEQ and the assessments by attending doctors and patients themselves. In the LDH group, there were poor correlations between JOABPEQ and assessments by doctors or patients, and there was a tendency toward fewer correlations at 12 months than at 6 months after surgery, even though there was a significant correlation in each functional category at 3 months after surgery[6].

As for the poor correlations shown by LDH patients 12 months after surgery, it might be associated with the fact that more than half of the LDH patients acquired the full mark at both 6 and 12 months after surgery in three functional domains (low back pain, lumbar function and walking ability). The limitations of this study are the small number of the LDH patients and the short follow-up duration. Further studies with a 2-year postoperative follow-up are needed.

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ORIGINAL ARTICLE

Matrix metalloproteinase 13 in the ligamentum flavum from lumbar spinal canal stenosis patients with and without diabetes mellitus

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Abstract
Background Lumbar spinal canal stenosis (LSCS) is one of the most common spinal disorders in the elderly, and ligamentum flavum (LF) hypertrophy is an important cause of LSCS. Matrix metalloproteinase 13 (MMP13) can degrade fibrillar collagens and elastic microfibrils, and is involved in inflammation and fibrosis. The purpose of this study was to compare the expression of MMP13 in the LF from LSCS patients with diabetes mellitus [DM (+)] with that in the LF from patients without DM [DM (−)] and to analyze the relationship among DM, MMP13 expression, and LF hypertrophy.
Methods LFs from 11 DM (+) and 24 DM (−) LSCS patients were analyzed in this study. Histology analysis using hematoxylin and eosin and Masson's trichrome stain was performed for each LF. The expression of MMP13 was analyzed by quantitative real-time PCR. The thickness of LF was measured by CT.
Results In the LF from DM (+) LSCS patients, the elastic fibers were more disorganized and had lower volumes than in the LF from DM (−) LSCS patients, while more fibrotic tissue was observed in the LF from DM (+) than from DM (−) LSCS patients. MMP13 expression was significantly higher in the LF from DM (+) LSCS patients (0.46 ± 0.61 vs. 0.05 ± 0.09, $P = 0.002$). The LF from the DM (+) LSCS patients was significantly thicker than that from the DM (−) LSCS patients (5.0 ± 0.9 vs. 3.1 ± 0.8 mm, $P < 0.01$), and the thickness was correlated with the expression of MMP13 (correlation coefficient = 0.43, $P = 0.01$, Pearson's correlation test).
Conclusion DM-related MMP13 expression can be one of the factors contributing to fibrosis and hypertrophy of the LF. Further research on the mechanism of this process may lead to new therapies for LF hypertrophy.

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Introduction

Lumbar spinal canal stenosis (LSCS) is one of the most common spinal disorders in the elderly. The causes of LSCS include ligamentum flavum (LF) hypertrophy, hypertrophy of the facet joints, bulging of the intervertebral discs, and vertebral endplate osteophytosis. Among them, LF hypertrophy plays a dominant role in the narrowing of the lumbar spinal canal [1]. In the lower lumbar spine, the LF is composed of thick elastic fibers that are densely arranged with interspersed collagen fibers [2]. Histological changes in the hypertrophied LF from LSCS patients include fibrosis, degradation of elastic fibers with an increase in collagen fibers, granulation tissue proliferation, chondroid metaplasia, and calcification [3–6]. Fibrosis is considered to be the main cause of LF hypertrophy, and transforming growth factor (TGF)-β released by endothelial cells may stimulate the fibrosis, especially during the early phase of hypertrophy [3]. However, the pathomechanism of LF hypertrophy remains unclear.

The matrix metalloproteinases (MMPs) include over 20 zinc-dependent enzymes that degrade or modify

extracellular matrix molecules, such as elastin, collagen, and proteoglycans [7, 8]. Several recent studies have demonstrated a role of MMP3 [9] or MMP inhibitors in the pathology of LF [10].

Of the MMPS, MMP13 can degrade fibrillar collagens, including type I, II, and III collagens, into gelatin. It can also degrade the elastic microfibrils that are involved in extracellular matrix remodeling [11]. In addition, MMP13 plays a role in inflammatory and fibrotic processes [12–14]. MMP13 was reported to be more highly expressed in the LF of LSCS patients than in that of disc herniation patients, and is expressed in LF fibroblasts [15]. Moreover, high plasma glucose increases the expression of MMP13 in vessels [16] and the cornea [17].

We hypothesize that diabetes mellitus (DM) can cause an increased expression of MMP13 in the LF, which may lead to fibrosis and extracellular matrix remodeling and finally cause LF hypertrophy. The purpose of this study was to compare the expression of MMP13 in the LF of LSCS patients with DM [DM (+)] with that in the LF of patients without DM [DM (−)] and to analyze the relationship among DM, MMP13 expression, and LF hypertrophy.

Materials and methods

Thirty-five LF samples were obtained from 35 LSCS patients who underwent decompressive laminectomy for neurogenic claudication. The demographic data of the patients are shown in Table 1. All patients gave informed consent to participate in this study, and the study was approved by the Institutional Review Board of our institute. The mean age was 76.7 ± 7.6 years in the DM (+) group and 72.6 ± 7.4 years in the DM (−) group. There was no difference in age or gender between the two groups ($P > 0.05$). CT images of the lumbar spine of 1 mm thickness were made for all the patients before surgery.

Histologic analysis with hematoxylin-eosin staining and Masson's trichrome staining

During surgery, the LF was removed en-bloc, and the epidural fat was detached. Half of each sample was immediately stored in a −80°C freezer for subsequent quantitative real-time PCR analysis; the other half was fixed in 4% neutral formalin and decalcified in 20% ethylenediaminetetraacetic acid (EDTA) for 4 weeks, then embedded in paraffin for histologic analyses. Two consecutive sections (4 μm thick) were cut on a microtome and subjected to hematoxylin-eosin (H&E) and Masson's trichrome staining, respectively. H&E staining was used to analyze the degradation of the elastic fibers, and Masson's trichrome staining was used to determine the degree of fibrosis [18]. Masson's trichrome staining exhibited elastic fibers as pink and collagen fibers as blue in color.

Paraffin sections of yellow ligament were stained with rabbit anti-MMP13 antibody (Abcam, no. ab39012) followed by Alexa488-conjugated goat anti-rabbit antibody (molecular probe) and TOTO3 (molecular probe) as a nuclear stain, and then observed under a confocal microscope (FV1000, Olympus).

Table 1 Demographic data of the patients

	DM (+)	DM (−)
Age (years)	76.7 ± 7.6 (range 67–84)	72.6 ± 7.4 (range 60–88)
Gender	Female 5, male 6	Female 12, male 12
Level	L2/3: 1, L3/4: 2, L4/5: 7, L5/S1: 1	L3/4: 3, L4/5: 20, L5/S1: 1

Quantitative real-time PCR

The total RNAs were isolated from LF samples by TRIzol reagent (Invitrogen Corp.), and the concentration and quality were determined with an ND-1000 spectrophotometer (NanoDrop). The first-strand cDNAs were synthesized using an Advantage RT-for-PCR kit (Clontech Laboratories Inc.), then subjected to real-time PCR analysis using SYBR Premix ExTaq II (Takara Bio Inc.) according to the manufacturer's instructions. The MMP13 mRNA was normalized to the β-actin mRNA in each sample. PCR amplification was carried out on a Thermal Cycler Dice Real-Time System (Takara Bio Inc.), and gene expression was quantified using the delta-delta Ct method [19]. Nucleotide sequences of the primers were as follows: MMP13 forward: 5′-GCCAGAACTTCCCAACCAT-3′, MMP13 reverse: 5′-GGGCCCAGAATTTTCTCC-3′, β-actin forward: 5′-TGAGCGCGGCTACAGCTT-3′, and β-actin reverse: 5′-TCCTTAATGTCACGCACGATTT-3′.

Measurement of LF thickness

The LF thickness was measured using the preoperative axial CT images. The thickness of the LF on both sides was measured at its midpoints at the level of the decompressed intervertebral disc, following the method proposed by Fukuyama et al. [20], using image-analysis software (Real INTAGE, Tokyo, Japan) that allowed digital measurements with a precision of 0.1 mm.

The measurements were repeated five times by the first author (G.C.), and the results were averaged. To assess the intra- and inter-observer reliability of measurements, CT images of LF from 20 patients were chosen in a random fashion and were measured again by the first author

2 weeks after his first measurement and by the second author (K.W.). The intra- and inter-observer reliability were statistically tested using an intraclass correlation coefficient. The data presented in the results section are based on the measurements by the first author.

Real-time PCR for *mmp13*

To evaluate the influence of glucose on mmp13 expression in fibroblasts, which are the main component of the LF, NIH3T3 fibroblastic cells from mice were cultured in serum-free Dulbecco's Modified Eagle's Medium (Sigma-Aldrich) for 24 h. Then cells were treated with or without 3 mg/ml glucose for 19 h. Subsequently, total RNA was isolated from NIH3T3 cells using an RNeasy mini kit (Qiagen, Hilden, Germany). Single-stranded complementary DNAs (cDNAs) were synthesized with reverse transcriptase (Clontech Laboratories, Palo Alto, CA). Real-time PCR was performed using SYBR Premix ExTaq II (Takara Bio Inc., Otsu, Shiga, Japan) with a DICE Thermal Cycler (Takara Bio Inc.), according to the manufacturer's instructions. *β-Actin* expression served as an internal control. Primer sequences were as follows:

mmp13-forward:	5′-AACCTGGACAAGCAGTTCCAAAG-3′
mmp13-reverse:	5′-GAAATGGCTTTTGCCAGTGTAGG-3′
β-actin-forward:	5′-TGAGAGGGAAATCGTGCGTGAC-3′
β-actin-reverse:	5′-AAGAAGGAAGGCTGGAAAAGAG-3′

Statistical analysis

All values were reported as mean ± standard deviation. All data were analyzed with the SPSS system (version 13.0). Comparisons between the two groups were made by the Mann-Whitney U test. The relationship between MMP13 expression and LF thickness was analyzed by Pearson's test. $P < 0.05$ indicated statistical significance.

Results

Hematoxylin-eosin staining

In the LF from DM (+) LSCS patients, the elastic fibers were fragmented, disorganized and focally lost, accompanied by a proliferation of collagen fibers (Fig. 1a, b), while, in the LF from DM (−) LSCS patients, rich elastic fibers were arrayed in parallel order (Fig. 1c, d).

Masson's trichrome staining

In the Masson's trichrome staining of the LF from DM (+) patients, a large area was stained blue, indicating the presence of massive fibrosis (Fig. 1e, f), whereas in the LF from DM (−) patients, a large area was stained pink and showed a regular arrangement, indicating a normal, non-fibrotic condition (Fig. 1g, h).

The immunostaining of MMP13 using the rabbit anti-MMP13 antibody exhibited enhanced expression of MMP13 in the LF from DM (+) patients compared with DM (−) patients (Fig. 2).

MMP13 expression measured by quantitative real-time PCR

The ratio of MMP13 to β-actin mRNA was 0.46 ± 0.61 (range 0.0009–1.5801) for the DM (+) group and 0.05 ± 0.09 (range 0.000001–0.403321) for the DM (−) group (Fig. 3). The MMP13 mRNA expression was significantly higher in the LF from the DM (+) patients than in that from the DM (−) patients ($P = 0.002$).

Thickness of the LF

The mean thickness of the LF measured on CT images was 5.0 ± 0.9 mm (range 3.5–6.7 mm) in the DM (+) group and 3.1 ± 0.8 (range 1.9–4.7 mm) in the DM (−) group (Fig. 4). The LF from DM (+) patients was significantly thicker than that from DM (−) patients ($P < 0.01$). For intra-observer reliability of measurements, the intra-class correlation coefficient was 0.991 (95% confidence interval 0.984–0.996). For the inter-observer reliability, it was 0.970 (0.944–984). Thus, both intra- and inter-observer reliability were acceptably high.

Correlation between MMP13 expression and LF thickness

A positive correlation was observed between the MMP13 expression and thickness of the LF both in DM (+) LSCS patients (correlation coefficient = 0.646, $P = 0.032$, Pearson's correlation test) and in DM (−) LSCS patients (correlation coefficient = 0.542, $P = 0.006$, Pearson's correlation test). Thus, the correlation coefficient was higher in DM (+) patients than in DM (−) patients.

mmp13 expression in NIH3T3 cells

mmp13 expression in NIH3T3 cells analyzed by real-time PCR was 1.50 ± 0.06 times higher in the cells cultured with glucose than in those cultured without ($P < 0.001$) (Fig. 5).

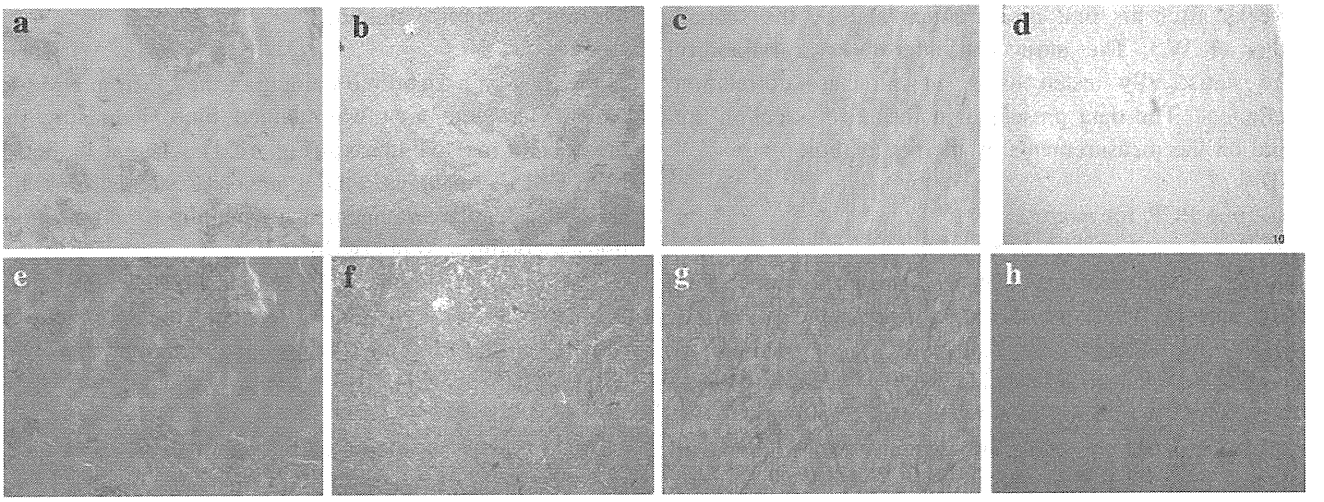

Fig. 1 **a** In the LF from DM (+) LSCS patients, elastic fibers were disorganized and focally lost, accompanied by a proliferation of collagen fibers. The elastic fibers also had low volumes and uneven diameters. H&E staining ×200. **b** LF from DM (+) LSCS patients. H&E staining ×40. **c** In the LF from DM (−) LSCS patients, a large area was stained pink with a regular arrangement, indicating a normal, non-fibrotic condition. H&E staining ×200. **d** LF from DM (−) LSCS patients. H&E staining ×40. **e** In the LF from DM (+) LSCS patients, a large area was stained blue, indicating the presence of massive fibrosis. Masson's trichrome staining ×200. **f** LF from DM (+) LSCS patients. Masson's trichrome staining ×40. **g** In the LF from DM (−) LSCS patients, rich elastic fibers were regularly arrayed, and the diameters of the elastic fibers varied only slightly. Masson's trichrome staining ×200. **h** LF from DM (−) LSCS patients. Masson's trichrome staining ×40

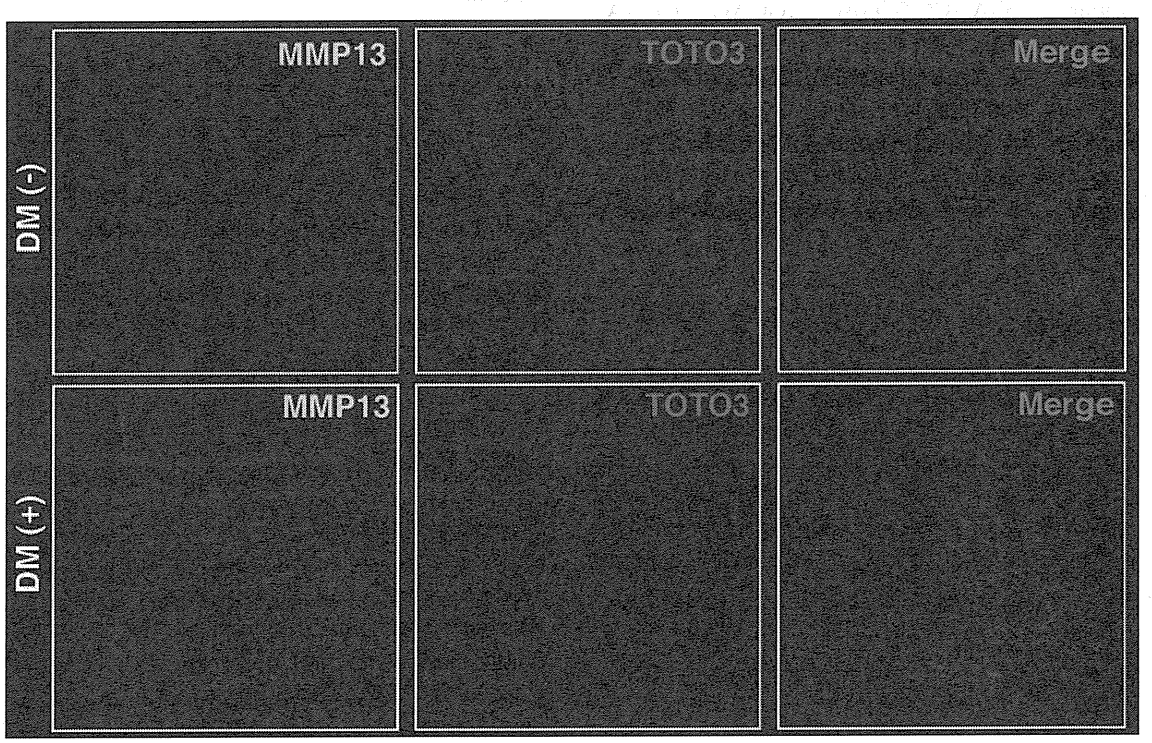

Fig. 2 Paraffin specimens of yellow ligament from individuals with DM [DM (+)] or non-DM [DM (−)] were stained with rabbit anti-MMP13 antibody followed by Alexa488-conjugated goat anti-rabbit antibody and observed under a confocal microscope. TOTO3 served as a nuclear stain

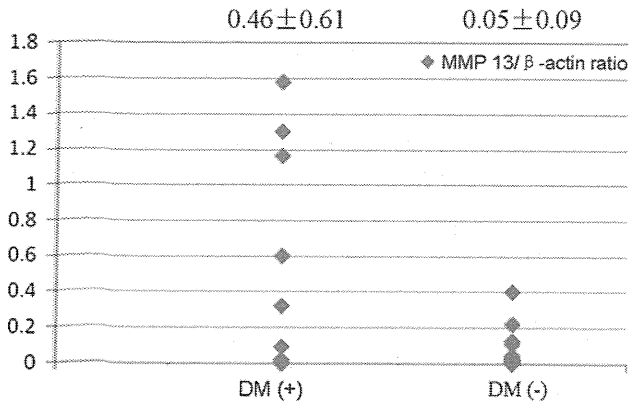

Fig. 3 Expression of MMP13 in the LF from DM (+) LSCS patients and DM (-) LSCS patients

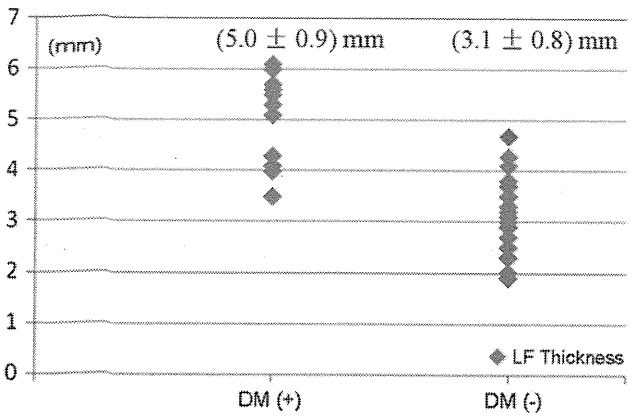

Fig. 4 Thickness of the LF from DM (+) and DM (−) LSCS patients

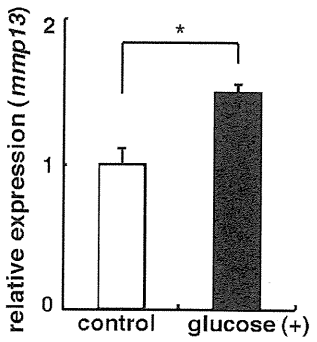

Fig. 5 NIH3T3 cells were cultured in the presence or absence of glucose (3 mg/ml) for 19 h, and *mmp13* expression was analyzed by real-time PCR. Data are shown as mean ± SD of *mmp13/β-actin* in cultured cells with glucose relative to that of without glucose. $*P < 0.001$

Discussion

In this study, we found an increased expression of MMP13 in the LF from DM (+) LSCS patients compared with the LF from DM (−) LSCS patients. In addition, elastin degradation and fibrosis of the LF were more severe in the DM (+) LSCS patients than in the DM (−) patients, and the LF of the DM (+) LSCS patients was significantly thicker. Our results suggest that an increased expression of MMP13, which may be related to DM, can be one of the factors contributing to fibrosis and hypertrophy of the LF, resulting in the progression of stenosis of the lumbar spinal canal.

Previous studies showed that the LF in the lumbar region is rich in elastic fibers, whose principal components are elastin and fibrillin [2]. Fibrillin can be degraded by MMP13, which is an important process in connective tissue remodeling [9]. MMP13 has been described as a trigger for the activation of a positive MMP2 and MMP9 feedback loop in asbestos-induced pulmonary fibrosis in mice [12]. The importance of MMP13 in fibrosis has also been shown in reports on bleomycin-induced pulmonary fibrosis in rats [21] and systemic sclerosis in humans [22]. In vessels and cornea, high plasma glucose increases the expression of MMP13 [14, 15]. In this study, the expression of MMP13 in the LF was higher in DM (+) than in DM (−) LSCS patients, and the expression of MMP13 was correlated with the thickness of the LF. Expression of mmp13 was upregulated by the presence of glucose in mice fibroblastic-like cells. MMP13 degrades both collagen fibers and elastic fibers, and is highly involved in extracellular remodeling [7, 9]. Thus, high plasma glucose levels may increase the expression of MMP13 in the LF and cause fibrosis. However, the exact mechanisms of the upregulation of MMP13 in DM patients should be elucidated by further studies.

In conclusion, we found a higher expression of MMP13 in the LF from DM (+) LSCS patients than in the LF from DM (−) LSCS patients. In addition, the elastin degradation and fibrosis of the LF was more severe in DM (+) patients than in DM (−) patients. These results suggest that the increased expression of MMP13 associated with DM can be one of the factors contributing to LF fibrosis and hypertrophy.

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