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Chapter 7

Back pain's association with vertebral endplate signal changes in sciatica

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ABSTRACT

BACKGROUND CONTEXT

Patients with sciatica frequently experience disabling back pain. One of the proposed causes for back pain is Vertebral Endplate Signal Changes (VESC) as visualized by Magnetic Resonance Imaging (MRI).

PURPOSE

To report on VESC findings, changes of VESC findings over time and the correlation between VESC and disabling back pain in patients with sciatica.

STUDY DESIGN/SETTING

A randomized clinical trial with one year follow-up.

PATIENTS SAMPLE

Patients with 6-12 weeks sciatica who participated in a multicentre randomized clinical trial comparing an early surgery strategy to prolonged conservative care with surgery if needed.

OUTCOME MEASURES

Patients were assessed by means of the 100-mm visual-analogue scale (VAS) for back pain (with 0 representing no pain and 100 the worst pain ever experienced) at baseline and one year. Disabling back pain was defined as a visual analogue scale score of at least 40mm.

METHODS

Patients underwent MRI both at baseline and after one year follow-up. Presence and change of VESC was correlated with disabling back pain using Chi-square tests and logistic regression analysis. This study was supported by a grant from the Netherlands Organisation for Health Research and Development (ZonMW) and the Hoelen Foundation, The Hague.

RESULTS

At baseline 39% of patients had disabling back pain. Of the patients with VESC at baseline 40% had disabling back pain compared to 38% of the patients with no VESC (P=0.67). The prevalence of type 1 VESC increased from 1% at baseline to 35% one year later in the surgical group compared to an increase from 3 to 11% in the conservative group. The prevalence of type 2 VESC decreased from 40 to 29% in the surgical group while remaining almost stable in the conservative group at 41%. The prevalence of disabling back pain at one year was 12% in patients with no VESC at one year, 16% in patients with type 1 VESC, 11% in patients with type 2 VESC and 3% in patients with both type 1 and 2 VESC (P=0.36). Undergoing surgery was associated with increase in the extent of VESC (Odds ratio [OR] 8.6, 95% CI

4.7-15.7, P<0.001). Patients who showed an increase in the extent of VESC after one year did not significantly report more disabling back pain compared to patients who did not show any increase (OR 1.2, 95% CI 0.6-2.6, P=0.61).

CONCLUSION

In this study undergoing surgery for sciatica was highly associated with the development of VESC after one year. However, in contrast with the intuitive feeling of spine specialists, those with and those without VESC reported disabling back pain in nearly the same proportion. Therefore VESC does not seem to be responsible for disabling back pain in patients with sciatica.

INTRODUCTION

Sciatica, more accurately called lumbosacral radicular syndrome, is one of the most common lumbar-spine disorders. The natural history of sciatica is favorable, with spontaneous resolution of the leg pain within 8 weeks in the majority of patients.[1] About 20 to 30% of the patients with sciatica receives surgery.[2] However, contrary to what one might expect given the advancements in diagnostic imaging and surgical techniques, the results after lumbar disc surgery for patients with radiculopathy due to a herniated disc do not seem to have improved during recent decades. Both classical and recent randomized controlled trials demonstrated that during longer follow-up at least 15-35% of the patients has an unsatisfactory outcome.[3-10] One of the most persistent accompanying complaints is chronic low back pain.[9, 11, 12] A considerable proportion of the costs and suffering due to sciatica can be attributed to the minority of patients that continues to experience symptoms like back pain.[12, 13] The identification of determinants of back pain and factors that promote persisting of back pain would be valuable as low back pain increasingly poses an economic burden to industrialized society, mainly in terms of the large number of work days lost.[13-15]

In the search for causes of associated back pain in patients with sciatica, vertebral endplate signal changes (VESC) visualized by Magnetic Resonance Imaging (MRI) have been proposed as a possible cause. In 1988 Modic described three types of signal changes.[16, 17] Type 1 lesions, hypointense on T1-weighted images and hyperintense on T2-weighted images, represent marrow edema, and are associated with an acute process.[16, 18, 19] Type 2 lesions, the most common type, have increased signal on T1 weighted images and isointense or slightly hyperintense signal on T2 weighted images, and represent fatty degeneration of subchondral marrow and are associated with a chronic process.[16, 20] Type 3 lesions, hypointense both on T1- and T2-weighted sequences, are considered to correlate with subchondral bone sclerosis.[16, 21]

The prevalence of VESC varies greatly among studies ranging from less than 1% in adolescents from the Danish general population[22] to 100% in selected patient populations.[23] Some studies observed an association between VESC and back pain,[24-27] while other studies did not observe any association.[28-31] Studies correlating VESC on consecutive MRIs in patients with sciatica are limited, especially studies comparing surgery with conservative treatment for the development of VESC. The determination of the clinical relevance of VESC is meaningful as accompanying endplate changes in patients suffering from radiculopathy due to a disc herniation are a frequent surgical indication to perform, in addition to the usual disc surgery for the radiculopathy, a fixation of two or more vertebrae in the lower spine or replacing the disc by a prothesis.[32-35] Lack of evidence and guideline consensus did result in a global problem of practice variation with regard to spinal surgery.[36, 37]

The investigators previously reported the results of a randomized controlled trial comparing early surgery with prolonged conservative care for patients with sciatica.[38] The trial showed faster recovery after early surgery, but the overall 1-year functional recovery rate was similar.

As the study protocol reported, patients underwent an MRI both at baseline and one year after randomization.[38] We now report on VESC findings, changes of VESC findings over time and the correlation between VESC findings and back pain in sciatica.

METHODS

STUDY POPULATION

Patients for this study were participants in a multicentre randomized trial among patients with 6-12 weeks sciatica (n=283). Patients were included only if they had a dermatomal pattern of pain distribution with concomitant neurological disturbances that correlated to the same nerve root being effected on MRI.[38] An early surgery strategy was compared to prolonged conservative care for an additional 6 months followed by surgery for patients who did not improve or who did request it earlier because of aggravating symptoms. The surgical treatment was standardized in this study (the symptomatic disk herniation was removed by a minimal unilateral transflaval approach with magnification. The goal of surgery was to decompress the nerve root and reduce the risk of recurrent disk herniation by performing an annular fenestration, curettage, and removal of loose degenerated disk material from the disk space with the use of a rongeur). Patients underwent MRI at the time of the initial diagnosis of sciatica and after one year of follow-up.[38] The medical ethics committees at the nine participating hospitals approved the protocol. Written informed consent was obtained from all patients. Details of the design and study protocol were published previously.[38]

MRI PROTOCOL AND IMAGE EVALUATION

MRI scans were performed in all nine participating hospitals using standardized protocols tailored to a 1.5 Tesla scanner. Sagittal T1 and axial T1 spin echo images of the lumbar spine were acquired. In addition, T2 weighted sagittal and axial series, and contrast-enhanced (gadolinium-DTPA) T1 fat suppressed images were obtained.

Two neuroradiologists and one neurosurgeon independently evaluated all MR images according to a predefined protocol (Appendix Table S1). Definitions of imaging characteristics were based on the recommendations from the combined task forces of the North American Spine Society, the American Society of Spine Radiology, and the American Society of Neuroradiology for classification of lumbar disc pathology.[39] VESC were defined according to criteria of Modic (as defined in the introduction).[16, 17] The observers graded the extent of VESC using three categories: mild, moderate and severe. As studies did not observe any VESC at level L1-L2,[21] all three observers only evaluated images from L2-L3 through L5-S1. Observers also evaluated the presence of Schmorl's nodes (herniation of the disc into the vertebral-body end plate). The observers were not provided any clinical information and have not been involved in the selection or care of the included patients. Observer experience in reading spine MRIs was

Table 1 Baseline characteristics of the intention-to-treat groups and the as-treated groups. Values are n (%) or means ± SD. N=263

	Intention to treat		As treated	
	Randomized to early surgery (N=129)	Randomized to prolonged conservative care (N=134)	Received surgery (n=168)	Received no surgery (n=95)
Age	41.7±10.0	43.2±9.3	41.9±9.8	43.5±9.3
Male sex	84 (65)	95 (71)	111 (66)	68 (72)
Body-mass indexò *	26.0±4.1	25.6±3.3	26.2±3.9	25.1±3.4
Duration of sciatica in weeks	9.5±2.4	9.6±2.2	9.5±2.4	9.6±2.1
Smoking	51 (40)	47 (35)	65 (39)	33 (35)
Vertebral Endplate Signal Changes (VESC)				
No VESC	82 (64)	69 (51)	99 (59)	52 (55)
VESC Type 1	2 (2)	2 (1)	1 (1)	3 (3)
VESC Type 2	44 (34)	62 (46)	67 (40)	39 (41)
VESC Type 3	0 (0)	0 (0)	0 (0)	0 (0)
VESC Type 1 and 2	1 (1)	1 (1)	1 (1)	1 (1)
Suspected disc level and type of displacement on MRI				
L3L4 Herniation	5 (4)	4 (3)	7 (4)	2 (2)
L4L5 Herniation	58 (45)	50 (37)	70 (42)	38 (40)
L4L5 Bulging	2 (2)	1 (1)	3 (2)	0 (0)
L5S1 Herniation	63 (49)	77 (57)	87 (52)	53 (56)
L5S1 Bulging	1 (1)	2 (2)	1 (1)	2 (2)
MRI assessed nerve root compression				
Definite	80 (62)	94 (70)	110 (65)	64 (67)
Probable	35 (27)	29 (22)	42 (25)	22 (23)
Possible	11 (9)	10 (7)	13 (8)	8 (8)
Definitely no root compression	3 (2)	1 (1)	3 (2)	1 (1)
Weeks between baseline and follow-up MRI	53.4±3.1	52.7±3.8	53.0±3.7	53.1±3.2
Roland Disability score ‡ *	16.3±4.4	16.1±4.0	16.7±4.2	15.4±4.1
VAS leg pain in mm § *	66.7±20.1	63.3±21.2	67.1±20.0	61.2±21.5
VAS back pain in mm §	33.6±29.5	30.5±27.1	33.9±30.4	28.7±23.9

Values are n (%) or means ± SD. N= 263.

No significant baseline differences were observed in the intention-to-treat group

* $P<0.05$ for the difference in the as-treated group

ò Body-mass index is the weight in kilograms divided by the square of the height in meters

‡ The Roland Disability Questionnaire for Sciatica is a disease-specific disability scale that measures the functional status of patients with pain in the leg or back. Scores range from 0 to 23, with higher scores indicating worse functional status.

§ The intensity of pain is indicated on a horizontal 100 mm visual analogue scale (VAS) with 0 representing no pain and 100 the worst pain ever experienced.

Table 2 Detailed description of the alteration of Vertebral Endplate Signal Changes (VESC) types between baseline and one year in the surgical and conservative group.

	Received surgery (n=168)	Received no surgery (n=95)
No change in VESC type between baseline and one year	55 (33)	78 (82)
Change from no VESC at baseline to		
VESC Type 1 at one year	50 (30)	5 (5)
VESC Type 2 at one year	22 (13)	7 (7)
VESC Type 1 and Type 2 at one year	13 (8)	1 (1)
Change from VESC type 1 at baseline to VESC Type 2 at one year	2 (1)	0 (0)
Change from VESC type 2 at baseline to		
VESC Type 1 at one year	7 (4)	2 (2)
VESC Type 1 and 2 at one year	7 (4)	0 (0)
Different changes: at one endplate change from no VESC to VESC Type 1 and at another endplate change from VESC type 2 at baseline to VESC Type 1 at one year	9 (5)	1 (1)
Otherwise	3 (2)	1 (1)

Values are n (%)

7 and 6 years post-residency for the neuroradiologists and 4 years post-residency for the neurosurgeon. The observers hold senior positions in busy spinal clinics with a focus on advanced spine surgery, and are confronted with spinal MRIs on a daily basis.

OUTCOME

Patients were assessed by means of the 100-mm visual-analogue scale (VAS) for back pain (with 0 representing no pain and 100 the worst pain ever experienced) and a 7-point Likert self-rating scale of global perceived recovery ranging from completely recovered to much worse. The outcome measures were assessed at baseline, 2, 4, 8, 12, 26, 38 and 52 weeks. The patients did not see the results of earlier assessments and were also blinded to the MRI results.

STATISTICAL ANALYSIS

The majority opinion of the two neuroradiologists and neurosurgeon regarding the different MRI characteristics (answer independently given by minimum 2 out of 3 observers) was used in the statistical analysis. In the cases all three observers gave a different answer (e.g. observer A reported no VESC, observer B VESC Type 1 and observer C VESC Type 2), an additional senior neurosurgeon (15 years post-residency experience) independently evaluated the cases of disagreement, and his opinion regarding the VESC type was subsequently used in the statistical analysis. Interreader agreement between the three observers for the baseline and one year follow-up images was assessed with absolute percentages of agreement and kappa coefficients. At the design phase it was pre-specified that kappa values would be calculated only for findings

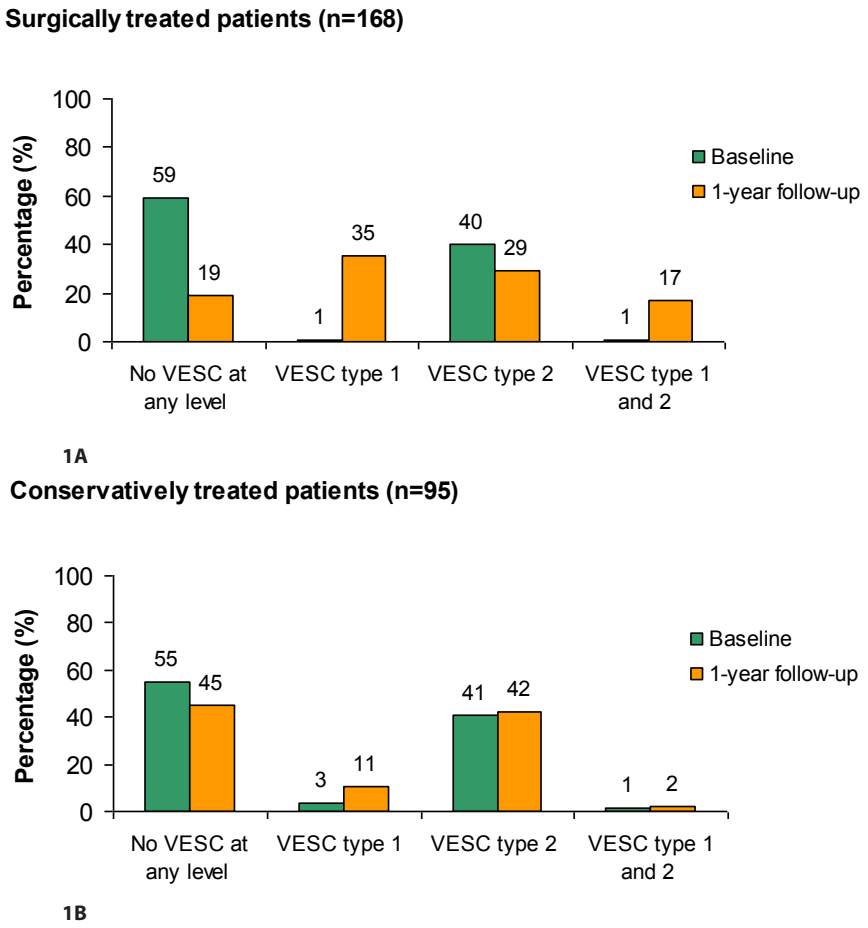


Figure 1 Prevalence of Vertebral Endplate Signal Changes (VESC) types at baseline and one year later in **1A)** surgically treated patients and **1B)** conservatively treated patients.
Analysis based on the "as-treated" groups.

reported in more than 10 and less than 90% of all reports[40] since the kappa statistic is affected by the prevalence of the events, so that findings with very high or low prevalence lead to very low kappa values, even if the observer agreement is high.[41, 42]

Disabling back pain was defined in the research group consensus meeting as a VAS for back pain of at least 40 mm, as this cutt-off value is regularly used when the VAS is categorized into favorable and unfavorable outcome.[43, 44] Perceived recovery on the 7-point Likert scale was defined as "complete" or "nearly complete recovery". The other (five) categories corresponded to "unsuccessful recovery".

Baseline and follow up characteristics of the surgical and conservative treatment group were compared using Student's t-test for continuous data and Chi-square tests for categorical data. Logistic regression analysis (univariate and multivariate analysis) was used to determine which

Table 3 Factors associated with presence of Vertebral Endplate Signal Changes (VESC) at one or more lumbar levels at baseline (n=263).

Association between general factors and VESC at any lumbar level	Comparison (%)	Univariate analysis			Multivariate analysis		
		OR	95%CI	P-value	OR	95%CI	P-value
VAS back pain	Per additional score	1.00	0.99-1.01	0.67			
Age	Per additional year of age	1.07	1.04-1.10	**<0.001**	1.06	1.03-1.09	**<0.001**
BMI	Per additional unit	1.04	0.97-1.11	0.29			
Gender	Male (68) vs female (32)	0.56	0.33-0.94	**0.029**	0.49	0.27-0.86	**0.013**
Presence of Schmorl's nodes at one or more lumbar level	Yes (11) vs no (89)	2.60	1.18-5.72	**0.017**	2.98	1.28-6.94	**0.012**
Presence of impaired discs at more than one level	Yes (79) vs no (21)	3.09	1.57-6.09	**0.001**	2.50	1.22-5.12	**0.012**

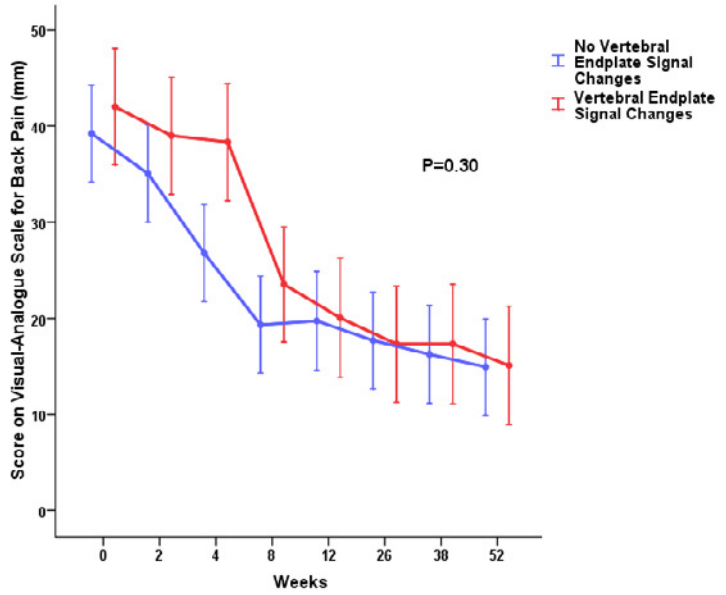
OR denotes odds ratio. CI denotes confidence interval.

baseline factors were associated with the presence of VESC at baseline. Repeated measurement analysis of variance was applied when analyzing differences in mean VAS-back pain during follow-up between patients with and without VESC. Since we specifically wanted to determine the influence of surgical treatment versus conservative treatment on progression of VESC, all analyses were performed according to the per-protocol analysis. As sensitivity analyses, we performed analysis excluding the cases in which all three MRI assessors disagreed on the VESC type. A P value of <0.05 was considered statistically significant.

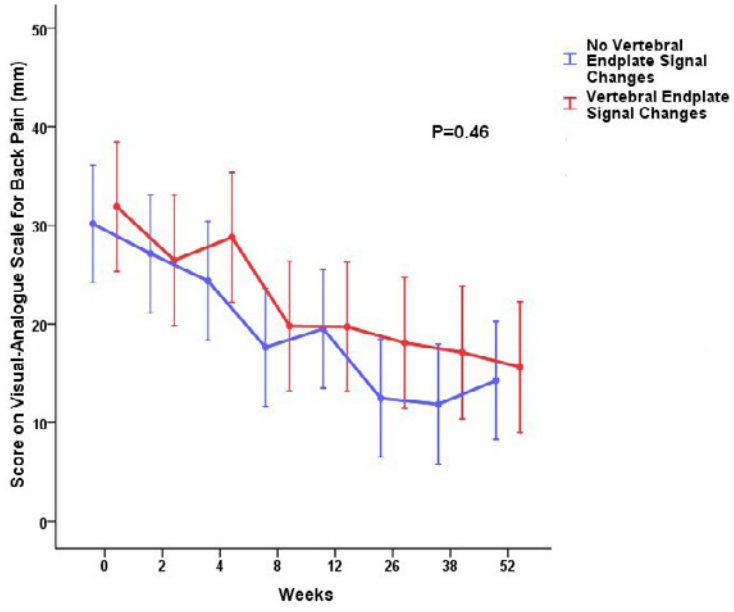
RESULTS

PATIENT CHARACTERISTICS

Of the 599 patients screened for the study, 283 patients were randomized. One year after randomization a second MRI was available for 267 (94.3%) of patients (Appendix Table S2). Baseline characteristics were similar among randomized patients for whom a second MRI was available compared to those for whom not. In total, 263 one-year MRIs could be evaluated properly due to the availability of both T1 and T2 images. Of the 263 patients who were eligible to be analyzed for the current study, 129 patients were randomized to early surgery and 134 to prolonged conservative care. Of the 129 patients randomized to early surgery, 15 recovered before surgery could be performed. Of the 134 patients assigned to prolonged conservative care, 54 eventually received surgery within the first year.

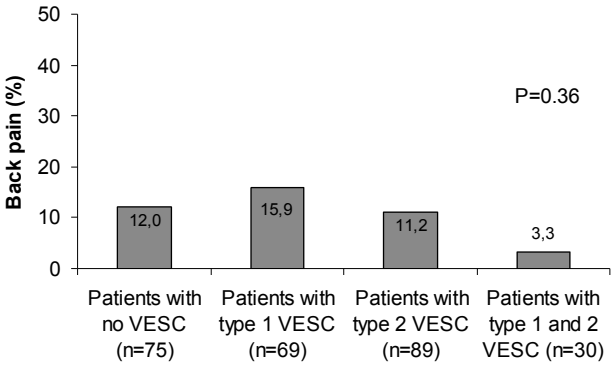


2A Surgically treated patients

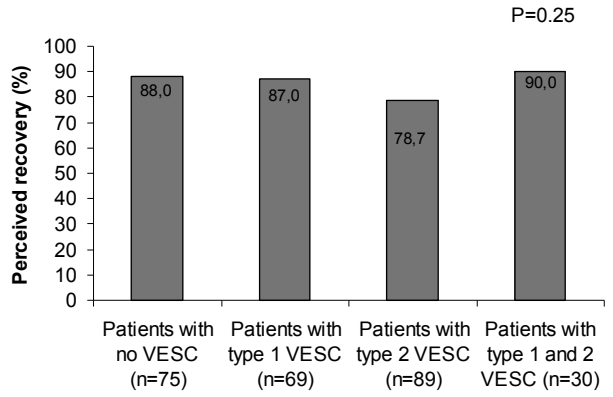


2B Conservatively treated patients

Figure 2 Repeated measurement analysis curve of Mean Scores for back pain on the Visual Analogue Scale. Sciatica patients with and without vertebral endplate signal changes on baseline MRI were compared. The vertical bars represent 95% confidence intervals.



3A



3B

Figure 3A) Disabling back pain *at one year* according to the type of Vertebral Endplate Signal Changes *at one year*. Disabling back pain was defined as a visual analogue scale score of at least 40mm on a scale of 0-100 (with 0 representing no pain and 100 the worst pain ever experienced)
3B) Perceived recovery *at one year* according to the type of Vertebral Endplate Signal Changes *at one year*. Recovery was defined as "complete" or "nearly complete recovery" on the 7-point Likert scale. The other (five) categories corresponded to "No recovery". VESC denotes Vertebral Endplate Signal Changes.

Absolute percentages of pairwise agreement among the three MRI observers for the presence and type of VESC varied from 75 to 99% (Appendix Table S3). As the prevalence of some VESC types were too low (< 10% of the reports) we did not calculate any kappa values for VESC. In 8 baseline MRIs and 9 one-year MRIs (3.4%) all three observers gave a different score regarding VESC type in the same patient (one reader no VESC, one reader VESC type 1 and one reader VESC type 2).

VESC FINDINGS AT BASELINE AND ONE YEAR FOLLOW-UP

At baseline, VESC were observed in 41% of 168 surgically treated patients compared to 45% of 95 conservatively treated patients (P=0.51). At baseline there was no difference in the types

of VESC between surgically and conservatively treated patients (P=0.39) (Table 1). When VESC were considered present at baseline, 91% in the conservative treatment group displayed VESC type 2 compared to 97% in the surgical group.

At one year follow-up, 67% of the patients who had undergone surgery altered in VESC type compared to 18% of the patients who were treated conservatively (P<0.001). In the surgical group the most common conversion was from no VESC to VESC type 1, while in the conservative group slightly more conversions were from no VESC to VESC type 2 (Table 2). The prevalence of VESC type 1 increased from a prevalence of 1% at baseline to 35% one year later in surgically treated patients compared to an increase from 3% to 11% in conservatively treated patients (Figure 1). The prevalence of VESC type 2 decreased from 40 to 29% in the surgical group while remaining stable at about 41% in the conservative group.

At one year follow-up, 67% of the patients of surgically treated patients showed an increase in the extent of VESC compared to 19% of conservatively treated patients (P<0.001, Appendix Figure S1). A decrease in the extent of VESC after one year was observed in a minority of patients: 2% of surgically treated patients displayed a decrease in VESC compared to 5% of the conservatively treated patients.

FACTORS ASSOCIATED WITH THE PRESENCE AND CHANGE OF VESC

The presence of VESC at one or more levels at baseline was significantly associated with increasing age, female gender, the presence of Schmorl's nodes and the presence of impaired disc levels at one or more levels (Table 3). Considering only the impaired disc level that was assumed by the observers to cause the lumbosacral radicular syndrome, the presence of VESC at this level was significantly associated with loss of disc height of the same disc level, female gender, presence of VESC at other levels and presence of Schmorl's nodes (Appendix Table S4). Undergoing surgery was significantly associated with increase in the extent of VESC between baseline and one year (OR 8.56, 95% CI 4.67-15.67, P<0.001).

CORRELATION BETWEEN VESC AND CLINICAL OUTCOME (DISABLING BACK PAIN AND RECOVERY)

At baseline, 40% of the patients with VESC had disabling back pain compared to 38% of the patients with no VESC (P=0.67). Of the patients with no or mild VESC at baseline 38% had disabling back pain compared to 41% of the patients with moderate to severe VESC (P=0.75). Patients who were surgically treated and displayed VESC at baseline reported higher VAS back pain scores during the first 8 weeks compared to surgically treated patients who had not displayed VESC at baseline, but after this short-term period the mean VAS back pain scores of these two groups converged (Figure 2).

At one-year follow-up, the prevalence of disabling back pain was 12% in patients with no VESC at one year, 16% in patients with type 1 VESC, 11% in patients with type 2 VESC and 3% in patients with both type 1 and 2 VESC (P=0.36) (Figure 3A). When stratifying according to received treatment during the first year also no significant differences in the prevalence of

disabling back pain existed between patients with the different types of VESC (Figure S2, P=0.29 in patients who had undergone surgery and P=0.93 in patients who had not undergone surgery). Of the patients with no or mild VESC at one year 11% had disabling back pain compared to 14% of the patients with moderate or severe VESC (P=0.39). Patients who showed an increase in the extent of VESC between baseline and one year did not significantly report more disabling back pain at one year compared to patients who did not show any increase in the extent of VESC (Odds ratio [OR] 1.21, 95% Confidence Interval [CI] 0.57-2.58, P=0.61).

Of the patients with VESC at one year 84% reported perceived recovery compared to 88% of the patients with no VESC (P=0.36). No significant differences in the prevalence of perceived recovery existed among patients with the different types of VESC (P=0.25) (Figure 3B). In addition, patients who showed an increase in the extent of VESC over one year did not significantly report less recovery compared to patients who did not show any increase in the extent of VESC (OR 1.57, 95% CI 0.79-3.11, P=0.20).

Sensitivity analyses to account for disagreement in VESC type yielded similar results (Figure S3). Also similar results were obtained when the analyses were stratified according to no VESC, VESC at one level and VESC at more than one level (Figure S4).

DISCUSSION

Undergoing disc surgery for sciatica was highly associated with progression in the extent of VESC compared to non-operative care in this study. In one year about two thirds of surgically and one fifth of conservatively treated patients displayed an increase of VESC. However, both at baseline and after one year follow-up, those with and those without VESC reported disabling back pain in nearly the same proportion. In addition, the proportion of patients reporting perceived recovery after one year was also nearly equally distributed between those with and without VESC. Therefore the results do present evidence that VESC are not responsible for disabling back pain in patients with sciatica. This remarkable scientific finding is in contrast with the intuitive intervention-prognostic diagnostic and treatment regimen of spinal physicians.

Studies correlating VESC to back pain in patients with sciatica are limited with conflicting results.[23] VESC have been reported to be associated with low back pain in the general population aged 40 years[26] and in working populations.[27, 45] Two studies did not observe more VESC among chronic low back pain patients compared to control subjects,[46] or between VESC and previous back pain in subjects without current back pain or sciatica.[31] Two earlier studies investigated the correlation between VESC and low back pain in patients treated for lumbar disc herniations, with contradictory results to the present study. Barth et al. evaluated MR images of 84 surgically treated patients for lumbar disc herniations.[47] Unfortunately the VESC were described by only one radiologist and MRI follow-up time ranged from 18 to 29 months.

After exclusion of reoperated patients, pre- and postoperative images were only available for 19 of 32 patients in the microdiscectomy group. Although back pain was significantly associated with progressive endplate changes, the clinical relevance of the association might be limited due to the relatively low observed spearman correlation coefficient (r=0.343).[48] No analysis was presented stratified according to VESC type. Albert et al. evaluated VESC in patients treated conservatively for sciatica.[20] Unfortunately the VESC were also described by only one radiologist. At 14 months follow-up, 60% of patients with VESC had self-reported back pain compared to 20% of patients without VESC. However, the proportion of patients with back pain did not significantly differ between the VESC types. Possibly, the results of the current study are contradictory with these two studies due to the definition of back pain. While they used self-reported back pain as the outcome we defined 'disabling back pain' based on patients' reported VAS for back pain.

The causes of VESC are not known. One theory is that toxic substances produced after damage of a disc invade the endplates and vertebral bones through micro fractures in the endplates and cause an inflammatory reaction.[49] Trauma to a disc by surgery causing the production of irritating substances may therefore accelerate the progression of VESC. The finding in this study of considerably more VESC in surgically treated compared to conservatively treated patients after one-year follow-up supports this theory. The extent of excision of the herniated disc might also be well correlated with the extent of the development of VESC. In support of this hypothesis is the study of Barth et al. who observed that patients who underwent standard discectomy (removal of herniated material plus discal tissue from the intervertebral space) developed significantly more VESC as compared to patients who underwent the less invasive sequestrectomy (only removal of the herniated material).[47]

The results of the present study are in line with previous studies showing a positive association between the prevalence of VESC with increasing age,[19, 21, 23] disc degeneration (loss of disc height, presence of impaired disc at more than one level)[17, 18, 23, 49] and Schmorl's impressions.[49] However, the finding of an association between female gender and VESC differs from previous findings in the literature showing no difference in the prevalence rates in relation to gender.[23] Two studies that examined VESC in unoperated sciatica patients did not provide any information regarding the relation of gender and prevalence of VESC.[20, 21] The current study finding should be confirmed by future research.

The most common VESC at baseline was VESC Type 2, a finding in concordance with previous studies in unoperated sciatica patients.[20, 21] The most common conversion in the surgical group was progression from no VESC at any level to type 1. In the study of Rahm et al. most patients developed VESC type 2 changes after lumbar discectomy.[50] However, contrary to the 12 months time interval between initial and follow-up MRI in this study, their interval varied from 32 to 59 months. In general it is agreed that VESC type 1 are unstable lesions which may convert to type 2 or back to normal.[51] The high observed prevalence of type 1 lesions at 12 months may still represent the more active stage of inflammation following disc surgery and

these lesions may convert to type 2 or back to normal over time. Furthermore, the observation that 81% of conservatively treated patients did not convert from one VESC type to another after one year is in concordance with longitudinal studies that investigated the natural course of VESC and have observed that 48% to 86% of people do not convert from one VESC type to another over periods of 14 to 72 months.[17, 19-21, 52]

An important limitation to be considered is that the study population consisted of sciatica patients raising the difficulty of generalizing the results to a population with back pain but without radicular symptoms. In general prevalence of VESC is higher in clinical than in non-clinical populations.[23] However, after one year the overwhelming majority of patients recovered from sciatic symptoms. Still patients exhibiting VESC at one year did not report more back pain compared to patients who did not display any VESC at one year. Also approximately 3% of the cases had three different VESC readings. However, similar results were obtained when those cases were left out of the analyses. Finally, the reported VESC and their relation with back pain were timed only once, one year after randomization. Although seemingly generalizable to other time points it is scientifically uncertain if we would have found comparable results at other moments.

In summary, in this one year follow-up study undergoing surgery for sciatica was highly associated with the development of VESC. However, both at baseline and after one year, those with and those without VESC reported disabling back pain in nearly the same proportion. Therefore the results indicate that VESC are not responsible for disabling low back pain in patients with sciatica and one should be reticent to offer back surgery based on MRI endplate changes.

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Table S1 MRI study variables

Disc level	Variable	Category
Separate for every end plate from level L2-L3 through L5-S1	Presence of vertebral end plate signal changes (VESC)	1. No VESC 2. VESC type 1: hypointense on T1-weighted sequences and hyperintense on T2-weighted sequences 3. VESC type 2: increased signal on T1 weighted sequences and isointense or slightly hyperintense signal on T2 weighted sequences 4. VESC type 3: hypointense both on T1- and T2-weighted sequences 5. VESC type 1 and 2
	Extent of vertebral endplate signal changes	1. mild 2. moderate 3. severe
	Presence of Schmorl's nodes (herniation of the disc into the vertebral-body end plate)	1. Yes 2. No
From level L1-L2 through L5-S1	Presence of impaired discs at more than one level	1. Yes 2. No
Disc level with the most severe nerve root compression	Disc level	1. Not applicable: no symptomatic disc level 2. L2L3 3. L3L4 4. L4L5 5. L5S1
	Loss of disc height at this level	1. Yes 2. No
	Signal intensity of nucleus pulposus on T2 images at this level	1. Hypointensity 2. Normal 3. Hyperintensity
	Disc contour at this level	1. Normal: no disc extension beyond the normal margins of the intervertebral disc space 2. Bulging: presence of disc tissue circumferentially (50-100%) beyond the edges of the ring apophyses 3. Consideration of a disc herniation: localized displacement of disc material beyond the normal margins of the intervertebral disc space
	Certainty about the presence of a disc herniation	1. Definite about the presence: no doubt about the presence 2. Probable about the presence: some doubt but probability > 50% 3. Possible about the presence: reason to consider but probability < 50% 4. Definite about the absence: no doubt about the absence of a disc herniation.

Table S1 (Continued)

Disc level	Variable	Category
	Probability of nerve root compression	1. Definite about the presence: no doubt about the presence 2. Probable about the presence: some doubt but probability > 50% 3. Possible about the presence: reason to consider but probability < 50% 4. Definite no clinical relevant nerve root compression

Table S2 One year after randomization a second MRI was available for 267 (94.3%) out of 283 participants. Reasons for why no second MRI at one year was available for the remaining 16 patients are listed in the Table.

Number of patients (total 16)	Reason why no second MRI was available one year after randomization
3	Stopped participating in the study after 8 weeks
1	Stopped participating in the study after 12 weeks
1	Stopped participating in the study after 16 weeks
1	Stopped participating in the study after 26 weeks
1	Did not show up on the scheduled appointment
1	Pregnancy
5	A second MRI was actually performed at 52 weeks, but we were not able to retrieve these MRIs. These 5 MRI's might have been lost during the storage process at the centers were the MRI's were performed or during the collection of the MRI's
3	Reason unknown

Table S3 Interobserver agreement regarding the type of Vertebral Endplate Signal Changes (VESC) and other MRI findings. The observers could choose from the following categories: No VESC, VESC type 1, VESC type 2, VESC type 3 and VESC type 1 and 2. A en B represent the neuroradiologists and C represents the neurosurgeon.
A) Interobserver agreement regarding the type of Vertebral Endplate Signal Changes (VESC)
B) Interobserver agreement regarding other MRI findings used in the current study
S3A

	A vs B		A vs C		B vs C		All observers	
	% agree-ment	kappa	% agree-ment	kappa	% agree-ment	kappa	% agree-ment	multi-rater kappa
Type of vertebral endplate signal changes upper endplate L2L3	98	*	98	*	99	*	97	*
Type of vertebral endplate signal changes lower endplate L2L3	97	*	96	*	97	*	96	*
Type of vertebral endplate signal changes upper endplate L3L4	95	*	96	*	97	*	94	*
Type of vertebral endplate signal changes lower endplate L3L4	96	*	96	*	97	*	94	*

Table S3 (Continued)

	A vs B		A vs C		B vs C		All observers	
	% agree-ment	kappa	% agree-ment	kappa	% agree-ment	kappa	% agree-ment	multi-rater kappa
Type of vertebral endplate signal changes upper endplate L4L5	84	*	85	*	87	*	80	*
Type of vertebral endplate signal changes lower endplate L4L5	84	*	84	*	87	*	79	*
Type of vertebral endplate signal changes upper endplate L5S1	75	*	79	*	77	*	69	*
Type of vertebral endplate signal changes lower endplate L5S1	75	*	81	*	76	*	69	*

***** Prevalence of some VESC types too low (< 10% of the reports) to calculate kappa values

S3B

	A vs B		A vs C		B vs C		All observers	
	% agree-ment	kappa	% agree-ment	kappa	% agree-ment	kappa	% agree-ment	multi-rater kappa
Presence of Schmorl's nodes§	78	0.20	79	0.41	83	0.24	70	0.28
Presence of impaired discs at more than one level§	93	0.80	84	0.60	84	0.60	81	0.66
Characteristic of the impaired disc level that was assumed to cause the sciatic symptoms								
Level¶	97	0.95	99	0.97	98	0.96	97	0.96
Loss of disc height§	99	*	73	0.27	74	0.29	72	0.34
Intensity of nucleus pulposus on T2 images at one or more levelsΨ	96	*	92	*	90	*	89	*
Nerve root compression‡	90	*	90	0.56	90	0.56	89	0.72

***** Since kappa values are afected by the prevalence of events, kappa values were only calculated for findings reported in more than 10% and less than 90% of all reports.

§ Categories were: yes versus no.

¶ The 5 categories were: 1) L2L3 2) L3L4 3) L4L5 4) L5S1

Ψ Categories were: 1) Hypointensity 2) Normal 3) Hyperintensity.

‡ Categories were: probability> 5% vs probability<50%.

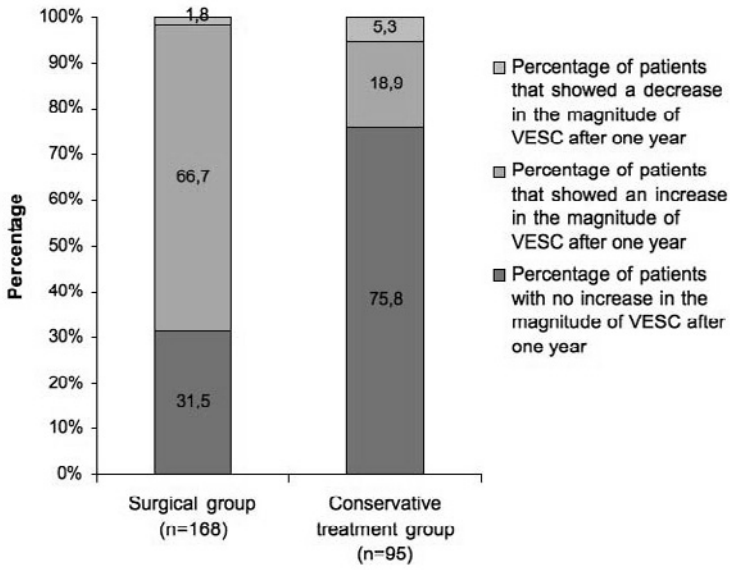
Table S4 Uni- and multivariate analysis to determine predictive value on the presence of Vertebral Endplate Signal Changes at the disc level that is assumed to cause the sciatic symptoms (n=263). OR denotes odds ratio. CI denotes confidence interval.

	Comparison (%)	Univariate analysis			Multivariate analysis		
		OR	95%CI	P-value	OR	95%CI	P-value
VAS back pain	Per additional score	1.00	0.99-1.01	0.42			

Table S4 (Continued)

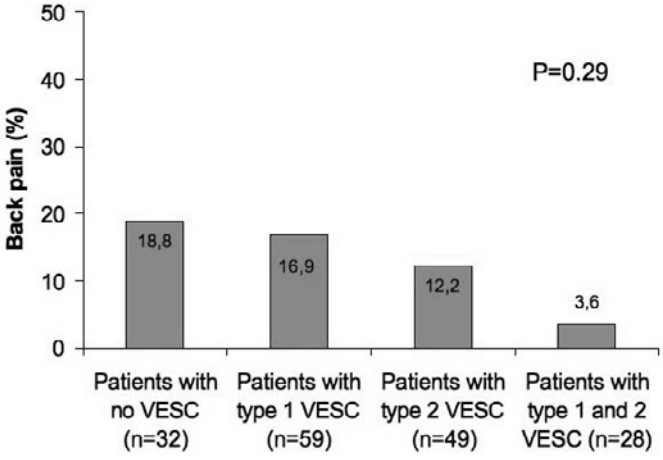
	Comparison (%)	Univariate analysis			Multivariate analysis		
Demographic variables							
Age	Per additional year	1.03	1.00-1.06	0.058			
Gender	Male (68) vs female (32)	0.44	0.26-0.76	**0.003**	0.46	0.26-0.81	**0.007**
MRI characteristics of the disc level that is assumed to cause the sciatic symptoms							
Disc level	L4L5 (44) vs L5S1 (56)	0.75	0.44-1.29	0.30			
Presence of Schmorl's nodes	Yes (5) vs no (95)	3.73	1.18-11.79	**0.025**	3.45	1.04-11.40	**0.042**
Loss of disc height at the disc level	Yes (91) vs no (9)	3.57	1.03-12.32	**0.044**	3.34	0.94-11.81	**0.062**
Signalintensity of nucleus pulposus on T2 images at one or more levels	Hypointens (91) vs normal (9)	2.24	0.73-6.83	0.16			
Presence of nerve root compression on MRI	Probability >50% (90) vs probability <50% (10)	0.98	0.40-2.37	0.96			
Presence of impaired discs at other disc levels	Yes (79) vs no (21)	1.72	0.87-3.40	0.12			
Presence of VESC at other disc levels	Yes (20) vs no (80)	2.12	1.14-3.93	**0.017**	1.99	1.04-3.83	**0.039**

Appendix Figure S1 Progression in the extent of VESC between baseline and one year in patients who underwent surgery and patients who received conservative care

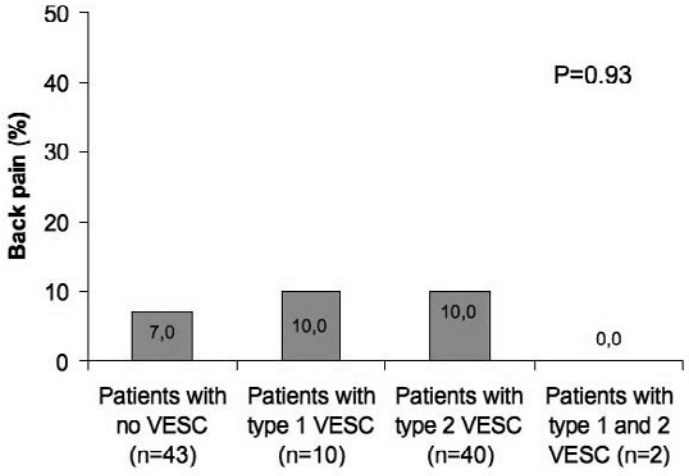


Appendix Figure S2 A) Disabling back pain *at one year* according to the type of Vertebral Endplate Signal Changes at one year in A) patients who underwent surgery during the first year and B) patients who underwent no surgery during the first year. Disabling back pain was defined as a visual analogue scale score of at least 40mm on a scale of 0-100 (with 0 representing no pain and 100 the worst pain ever experienced)

S2A Patients who underwent surgery during the first year

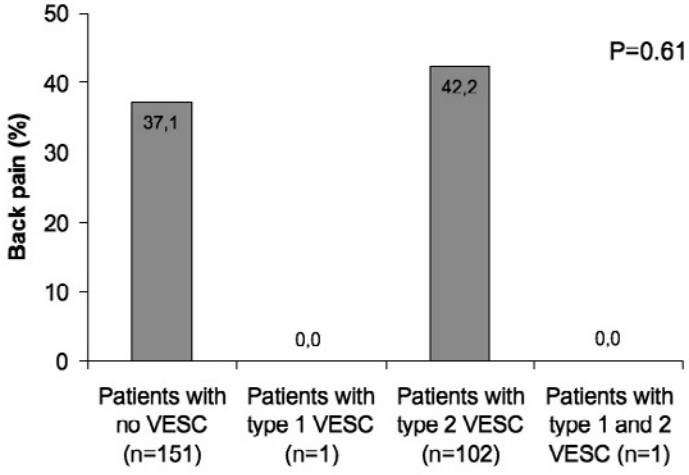


S2B Patients who underwent no surgery (conservative treatment) during the first year



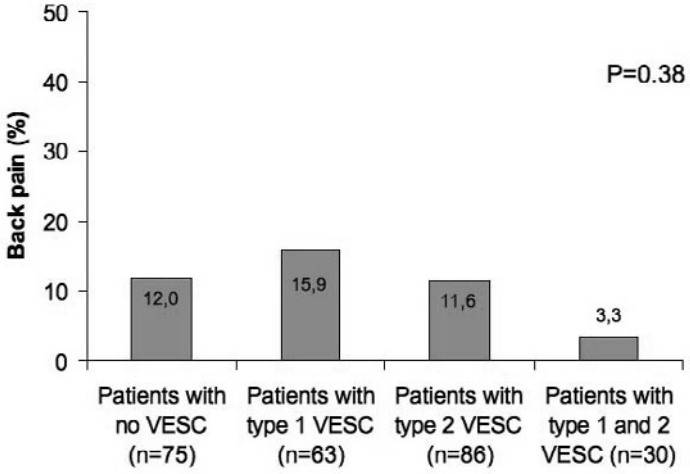
Appendix Figure S3 Disabling back pain at A) baseline and B) one year according to the type of Vertebral Endplate Signal Changes (VESC). This analysis only included patients in whom at least 2 out of the 3 MRI readers gave the same score regarding VESC type.

S3A Baseline (n=255).



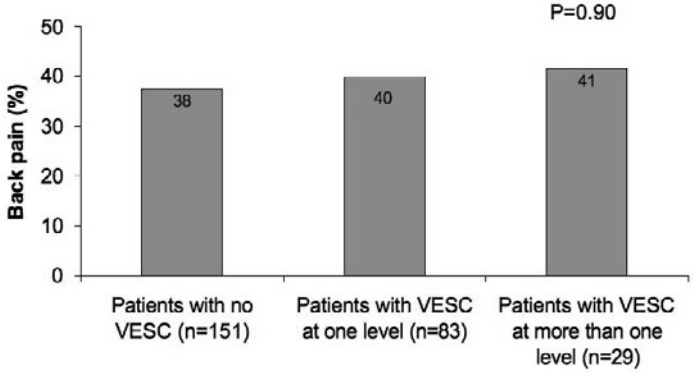
At baseline only 1 patient displayed VESC type 1 and 1 patient VESC type 1 and 2

S3B One-year follow-up (n=254)



Appendix Figure S4 Disabling back pain at A) baseline and B) one year according to Vertebral Endplate Signal Changes (VESC) at one or more levels.

S4A Baseline



S4B One-year follow-up