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REVIEW

Vertebral endplate signal changes (Modic change): a systematic literature review of prevalence and association with non-specific low back pain

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Abstract The prevalence of "vertebral endplate signal changes" (VESC) and its association with low back pain (LBP) varies greatly between studies. This wide range in reported prevalence rates and associations with LBP could be explained by differences in the definitions of VESC, LBP, or study sample. The objectives of this systematic critical review were to investigate the current literature in relation to the prevalence of VESC (including Modic changes) and the association with non-specific low back pain (LBP). The MEDLINE, EMBASE, and SveMED databases were searched for the period 1984 to November 2007. Included were the articles that reported the prevalence of VESC in non-LBP, general, working, and clinical populations. Included were also articles that investigated the association between VESC and LBP. Articles on specific LBP conditions were excluded. A checklist including items related to the research questions and overall quality of the articles was used for data collection and quality assessment. The reported prevalence rates were studied in relation to mean age, gender, study sample, year of publication, country of study, and quality score. To estimate the association between VESC and LBP, 2 × 2 tables were created to calculate the exact odds ratio (OR) with 95% confidence intervals. Eighty-two study samples from 77 original articles were identified and included in the analysis. The median of the reported prevalence rates for any type of VESC was 43% in patients with non-specific LBP and/or sciatica and 6% in non-clinical populations. The prevalence was positively associated with age and was negatively associated with the overall quality of the studies. A positive association between VESC and non-specific LBP was found in seven of ten studies from the general, working, and clinical populations with ORs from 2.0 to 19.9. This systematic review shows that VESC is a common MRI-finding in patients with non-specific LBP and is associated with pain. However, it should be noted that VESC may be present in individuals without LBP.

Keywords Systematic review · Modic changes · Vertebral endplate · Magnetic resonance imaging · Prevalence · Low back pain

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Introduction

Magnetic resonance imaging (MRI) is commonly used in the diagnosis of patients with low back pain (LBP) and sciatica [1]. In the search for causes of LBP, vertebral endplate signal changes (VESC) have come into focus. The most commonly used definition of VESC in the literature is from a study of 474 patients with non-specific back pain by Modic et al. [106], who described two types of signal changes: types 1 and 2. From the same study, histological

examination performed on type 1 changes in three patients revealed fissured endplates and vascular granulation tissue adjacent to the endplates. In three patients with type 2 changes, disruption of the endplates as well as fatty degeneration of the adjacent bone marrow were observed [106]. Later, type 3 was described as corresponding to sclerosis on radiographs [105].

The prevalence of VESC varies greatly between the studies ranging from less than 1% [82] in adolescents from the Danish general population to 100% [41, 149] in selected patient populations. A large number of studies and narrative reviews have reported on VESC in patient populations with specific LBP (e.g. spondylitis, trauma, tumours and spondyloarthropaties) [55, 57, 64, 144]. VESC has also been investigated in patients with non-specific LBP. In studies of these patients, the association between VESC and LBP has been investigated, with the strength of association from none [96] to strong [154]. The wide range in the reported prevalence rates of VESC and the divergent associations with LBP could be explained by differences in the definitions of VESC and LBP. They could also be explained by differences in the study samples in relation to age, sex, and type of study population (i.e. clinical or non-clinical). Other factors that could also explain the difference in prevalence and association with LBP include year of publication, racial distribution in the study sample, and the overall quality of the study.

To our knowledge, there is no systematic critical review of the literature which addresses the prevalence of VESC and its association with non-specific LBP. Therefore, the overall aim of this study was to systematically review the current literature in relation to "vertebral endplate signal changes" (VESC) in the lumbar spine as seen on magnetic resonance imaging. The specific questions that we wanted to answer were:

1. What is the prevalence of VESC in the absence of specific pathology in relation to:
a. Age?
b. Sex?
c. Study sample?
d. Year of publication?
e. Country of study?
f. Quality of study?
2. Is VESC associated with LBP?

Materials and methods

Search strategy

The MEDLINE, EMBASE, and SveMED databases were searched for the period 1984 to November 2007. Because MRI was not commonly used in a clinical setting before 1984, our search was restricted to the period after 1984. The following terms were searched for as a MeSH term and/or as free text, "MRI", "vertebral endplate", and "lumbar spine". For the purpose of inclusion of relevant articles, we defined VESC as "signal-changes seen on MRI in the vertebral bone, extending from the endplate" [63]. This definition allowed us to describe VESC regardless of aetiology. Also using this definition, articles that described signal changes only present in the bone marrow were excluded.

Definition of quality criteria

The clarity of the articles was assessed on the basis of a set of minimum criteria that the authors considered to be essential for the purpose of this review (Table 1). These items related to (1) the specific research questions (age, sex, year of study, country of study, and study sample) and (2) the overall quality of the article. The items for quality assessment were (a) those that were needed for other researchers to reproduce the study (external validity: population, age, and gender) and (b) those that were needed to ensure quality of the imaging results (internal validity: MR field strength, availability of T1-weighted and T2-weighted MRI sequences, definition of VESC, number and professional experience of observers, if observers were blinded to symptoms and other observers' MRI-readings, and the availability of results from reproducibility study). A checklist that included these items was made and used for data collection ("Appendix").

Review process

Articles that could be included were original articles written in English, French, German, Danish, Norwegian, Swedish, Finnish, or Russian. Articles to be excluded were (1) reviews, (2) case reports with less than ten patients, (3) comments/letters, (4) animal studies, (5) ex vivo studies, (6) in vitro studies, (7) double publications, and (8) studies that did not really investigate VESC. Furthermore, articles on specific diagnoses or conditions already defined as having an association with LBP were excluded (e.g. spondylodiscitis, ankylosing spondylitis). Studies on individuals with disc herniations with or without sciatica were eligible for review. In case articles had more than one study sample (e.g. case and control groups), these were treated as separate studies for the purpose of the data collection and analysis. The first author inspected all retrieved titles and abstracts and excluded those articles that met the exclusion criteria. After retrieval of the remaining articles in full text, all articles in English were read by two reviewers independently so that each article was read by both the first author and one of the other reviewers. Reference lists of the

Table 1 Criteria for quality assessment of study samples describing VESC

Type of information	Specific information
Study data (0–2 points)	Year of study (stated/not stated)
	Country of study (stated/not stated)
Descriptive data (0–5 points)	Population: clinical, general, working, asymptomatic, mixed (stated/not stated)
	Number of individuals (stated/not stated)
	Number of females and males (stated/not stated)
	Mean age (stated/not stated)
	Standard deviation of age or age range (stated/not stated)
MRI data (0–2 points)	Field strength (stated/not stated)
	T1 and T2 (yes/no)
Description of VESC (0–2 points)	Definition of VESC (yes/no)
	Subtypes (yes/no)
MRI evaluation (0–4 points)	Number of observers (stated/not stated)
	At least one radiologist as observer (yes/no)
	Observer blinded to symptoms (yes/no)
	Observer blinded to other observers readings (yes/no)
Reproducibility (0–2 points)	Reproducibility study performed (yes/no)
	Results of reproducibility study available (yes/no)
Total score: 0–17 points	Stated or yes = 1 point
	Not stated or no = 0 points

included articles were searched for additional articles. Articles in French and German were read by one reviewer only. Relevant data from each article were entered in checklists by each reviewer ("Appendix"). Furthermore, articles were screened for data that could be used to estimate an association between VESC and LBP. These articles were independently reviewed by authors 1 and 5 and relevant data were entered in new checklists. For each article, each pair of checklists was checked for consistency by the first author. In case of inconsistencies between two reviewers, the correct information was established through a second consensus reading by authors 1 and 5. Information from the checklists was transferred to a database using EpiData (The EpiData Association, version 3.1, Odense Denmark, 2006).

Data analysis

Variables of interest were transferred to a database in STATA (StataCorp, 2000, Stata Statistical Software: Release 8.2, Stata Corporation, College Station, TX, USA) for analyses.

The prevalence rates of VESC were reported in relation to the number of individuals and/or in relation to the number of affected lumbar disc levels. Studies that reported the prevalence in relation to both individuals and levels were included in both analyses. VESC could be defined as type 1, type 2, type 3, mixed types (more than one type situated in the same endplate [88] or within the same person [23]), and any type. The prevalence rates were studied in relation to (1) mean age, (2) gender, (3) study sample (non-LBP, general, working, and clinical populations), (4) year of publication, (5) country of study (Asia, North America, Europe, and other countries), and (6) quality score (0–17). These estimates were analysed visually through graphs and tested for linearity with robust linear regression. For comparison of median values between groups, the Wilcoxon rank-sum (Mann–Whitney) test was used. For comparison of mean values between groups, the indicator function for linear regression was used. A P level of 0.05 was considered significant. Two-by-two tables were created, where possible, to estimate the associations between VESC and LBP and presented as exact odds ratios (OR) with 95% confidence intervals (CI) in relation to age, study sample, and quality of study. In order to calculate exact OR in 2×2 tables that included zero in one of the cells, the median unbiased estimation method was used [58]. A positive association was defined as CI limits above 1.

Results

Review process

In all, 137 full text articles were reviewed (Fig. 1). Eight were written in German [8, 16, 56, 59, 69, 97, 134, 155], three in French [29, 30, 91], and the remaining articles being in English. There were inter-reader differences in the checklists in 28 cases (11 vs. author 2, 5 vs. author 3, 6 vs.

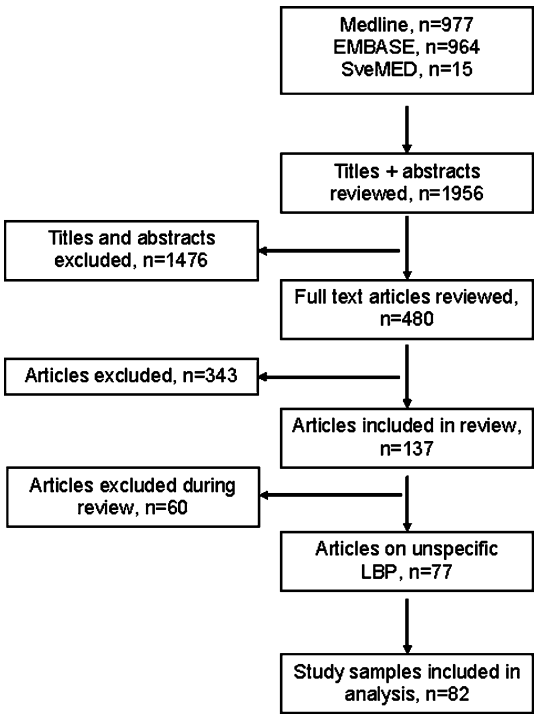

Fig. 1 Flow chart of the inclusion process of articles used in the review of the prevalence of vertebral endplate signal changes and its association with low back pain

author 4, and 6 vs. author 5). In all these cases, consensus was obtained without difficulties by authors 1 and 5.

A total of 60 papers were excluded after review; 27 as they dealt with specific LBP conditions (Table 2) and 33 for other reasons: one review article [55], four case reports [7, 27, 129, 148], one double publication [90], one of two studies reporting data from the same study sample [80], ten for evaluating signal changes other than those related to the endplate [6, 20, 51, 53, 71, 113, 116, 139, 146, 150], and eight articles because they did not report the exact numbers needed to calculate the prevalence rates of VESC [4, 10, 109, 110, 114, 122, 133, 141]. Finally, eight articles were excluded because the study samples were selected on the basis of the presence of VESC [41, 50, 56, 63, 68, 134, 137, 149]. In 9 of the remaining 77 original articles, a total of 21 study samples were investigated [24, 35, 36, 49, 74, 76, 78, 102, 145]. Seven of these represented specific LBP conditions and were excluded. The 14 study samples, which included patients with non-specific LBP ($n = 9$) or individuals from the non-clinical population ($n = 5$), were included. In total 82 study samples from 77 articles were included in the analysis.

Table 2 Articles on VESC in specific low back pain conditions excluded from the review

LBP condition	Reference number(s)
Spondylodiscitis	[11, 12, 34, 47, 48, 59, 70, 86, 93, 130, 152]
Spondyloarthropathy (e.g. ankylosing spondylitis)	[20, 65, 91, 92, 100, 103, 142, 155]
Schmorl's nodes	[60, 94, 135]
Fracture	[139, 151]
Spinal cord infarction	[157]
Other conditions	[42, 121]

What is the prevalence of VESC?

Of the 82 study samples for which the prevalence was investigated, 49 reported prevalence rates of VESC in individuals only, 24 in relation to lumbar levels only, and 9 in relation to both individuals and lumbar levels. The prevalence rate of specific subtypes of VESC was reported in 42 study samples. The median prevalence rates of any type of VESC in relation to individuals and lumbar levels were 36% ($n = 58$) and 14% ($n = 33$), respectively (Figs. 2, 3).

Age

Of the 67 study samples for which the mean age was reported, 48 reported the prevalence of VESC in individuals and 28 in relation to lumbar disc levels. A wide spread of prevalence rates was seen regardless of age although with a positive correlation with age. The estimated increase of the prevalence of VESC in individuals was 11% per 10 years ($P < 0.001$) (Fig. 4) and 6% per 10 years ($P < 0.03$) for lumbar levels (Fig. 5).

Sex

There was no difference in the prevalence rates of VESC in relation to sex in the 45 study samples that reported the

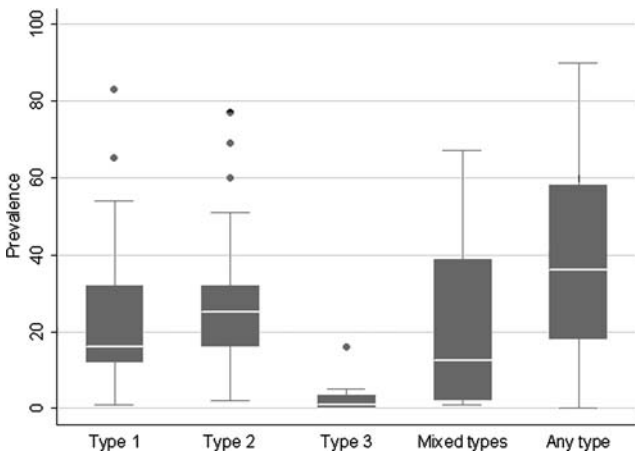

Fig. 2 Median and range of the prevalence rates of different types of vertebral endplate signal changes reported in relation to individuals in 58 study samples

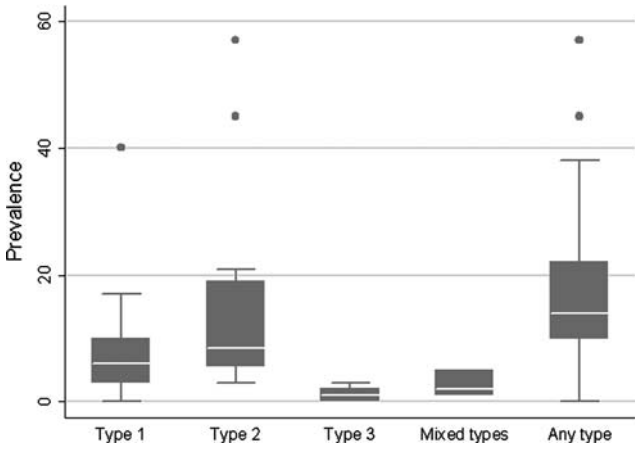

Fig. 3 Median and range of the prevalence rates of different types of vertebral endplate signal changes reported in relation to lumbar levels in 33 study samples

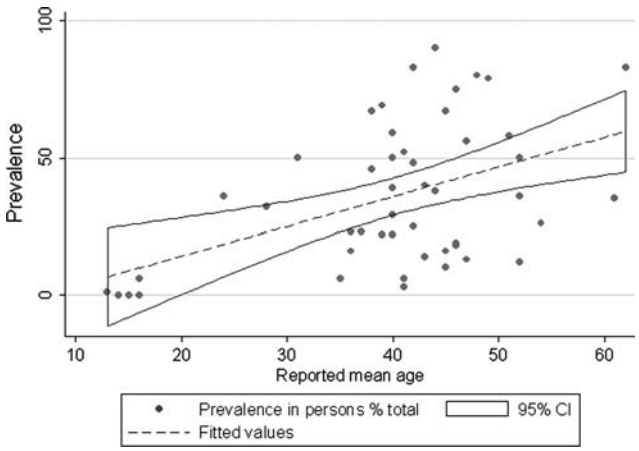

Fig. 4 Prevalence rates of vertebral endplate signal changes (any type) in relation to individuals by mean age in 48 study samples

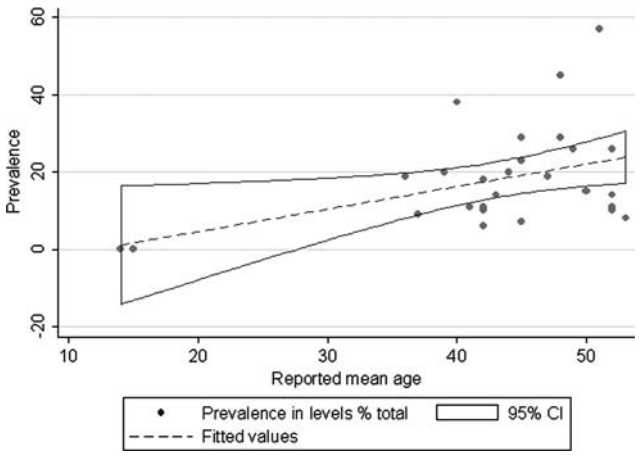

Fig. 5 Prevalence rates of vertebral endplate signal changes (any type) in relation to disc levels by mean age in 28 study samples

prevalence in individuals or in the 22 study samples that reported the prevalence in relation to levels (data not shown).

Study sample

Of the 58 study samples that reported the prevalence of VESC in individuals, 45 were from clinical populations, two from the general population [81, 82], four from the working population (including top athletes) [13, 17, 36, 88], and the seven study samples of the non-LBP populations were from six studies [24, 31, 38, 62, 78, 153]. The median prevalence of VESC was 6% in study samples of individuals without LBP ($n = 7$), 12% in the general population ($n = 2$), 6% in the working population ($n = 4$), and 43% in study samples from the clinical population ($n = 45$). Due to the small number of studies that reported prevalence rates from samples of non-clinical populations (non-LBP, general, and working), these three groups were treated as one in the analysis. The median prevalence of VESC in the 13 study samples from the non-clinical population (6%) was significantly less than that from the 45 study samples from clinical population (43%), $P < 0.0001$ (Fig. 6).

The median prevalence of VESC in relation to lumbar levels was 0% in non-LBP populations ($n = 3$), 12% in the general population ($n = 2$), 11% in the working population ($n = 4$) and 19% in study samples from clinical populations ($n = 24$). When the study samples from non-clinical populations were combined for the analysis, the prevalence of VESC in lumbar levels was 9% in non-clinical populations ($n = 9$) and 19% in clinical populations ($n = 24$), $P < 0.02$ (Fig. 7).

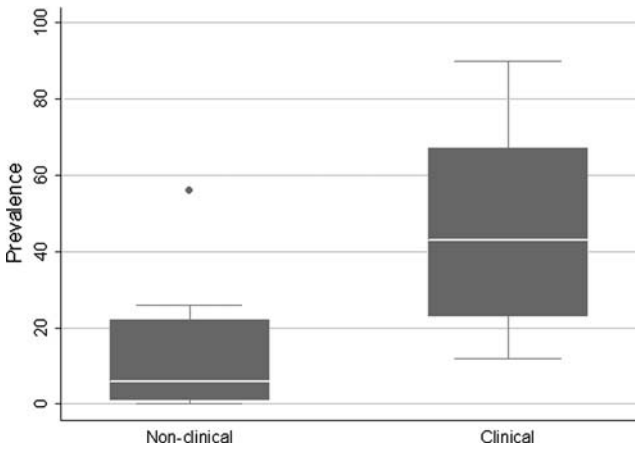

Fig. 6 Median and range of the prevalence rates of vertebral endplate signal changes in individuals, reported in 13 study samples from the non-clinical population and 45 study samples from the clinical population

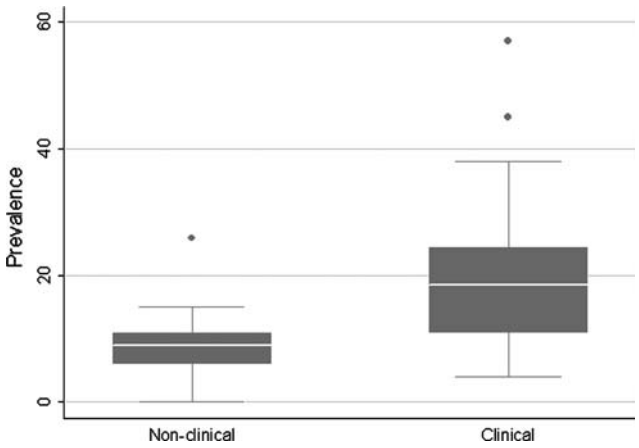

Fig. 7 Median and range of the prevalence rates of vertebral endplate signal changes in relation to levels, reported in nine studies from the non-clinical population and 24 studies from the clinical population

Year of publication

There was no association between the year of publication and the prevalence of VESC in study samples from which the prevalence rates were reported in relation to individuals ($n = 58$) or in relation to lumbar levels ($n = 33$) (data not shown).

Country of study

In relation to the prevalence of VESC in individuals, there was no difference in the mean prevalence between the three geographical regions Europe ($n = 33$), North America ($n = 17$), and Asia ($n = 8$) (data not shown). However, in the 33 study samples in which the prevalence rates were reported in relation to lumbar levels [Europe ($n = 22$), North America ($n = 9$), and Asia ($n = 2$)], the mean prevalence in studies from Europe (19%) was higher than that in studies from Asia (9%, $P < 0.05$), but not higher than that in studies from North America (15%).

Quality of study

The mean quality score (0–17) was 11.7 and only two [35, 81] (3%) of the 77 original articles included in the review met all quality criteria (Table 3). The criteria that most articles did not meet were related to the description of the MRI evaluation and the procedures concerning reproducibility.

For the 58 articles that reported the prevalence of VESC in individuals, there was a negative linear association between the prevalence and the quality score ($P < 0.001$) (Fig. 8). There was no association between the prevalence of VESC and the quality score in relation to lumbar levels (data not shown).

Is VESC associated with LBP?

There were ten studies from which data could be extracted to estimate the association between VESC and LBP (Table 4). A positive association could be estimated in three of the five studies that used provocative discography as the LBP outcome and in four of the five studies that used self-reported LBP as an outcome. The odds ratios for these seven studies ranged from 2.0 to 19.9. There was no difference in the association between LBP and the type of VESC in five studies of the ten studies where data were available to estimate an association [3, 18, 84, 126, 154].

Due to the small number of studies, it was not meaningful to investigate if there were differences in the association between VESC and LBP in relation to different study samples, quality of study, or age groups.

Discussion

To our knowledge, this is the first systematic critical literature review on VESC in relation to its prevalence and association with non-specific LBP.

Results from this review document that VESC is a common MRI-finding in patients with non-specific LBP with a median prevalence of 43% and it is less common in non-clinical populations with a median prevalence of 6%. Also, it is documented that the prevalence increases with age and it is more common in Europe than in non-European countries.

In this review, we found a positive association between VESC and LBP in the majority of studies reporting on this subject. According to a recent systematic review on the diagnostic accuracy of tests for low back pain [54], the presence of VESC increases the likelihood of having LBP during provocative discography. Our review that also included studies on self-reported LBP came to the same conclusion. The ORs for the studies that reported a statistically significant positive association ranged from 2.0 to 19.9, which is a relatively strong association. However, the confidence limits for these estimations were wide for the studies that used discography to provoke pain. Although the number of studies is small, it is important to note that a positive association between VESC and LBP has not only been found in the majority of studies of patients with LBP from different countries, but also in the general [81] and working [88, 126] populations. In other words, there is a considerable consistency in this association.

If VESC is a condition that causes LBP, it seems likely that the prevalence would be the highest in study samples of patients with LBP, lower in study samples from the general and working population and lowest in individuals without LBP. The present review did not identify such a

Table 3 Distribution of the quality score in relation to the 77 articles included in the review

Reference	Study data (0–2)	Descriptive data (0–5)	MRI data (0–2)	VESC definition (0–2)	MRI evaluation (0–4)	Reproducibility (0–2)	Total score per study (0–17)
Albert 2007[3]	1	3	2	2	2	0	10
Assheuer [8]	1	5	1	2	0	0	9
Aunoble [9]	2	5	1	1	0	0	9
Baranto [13]	2	5	2	2	2	0	13
Battie [14]	1	3	2	2	2	2	12
Becker [16]	2	5	2	2	2	0	13
Bennett [17]	1	5	2	2	3	0	13
Braithwaite [18]	1	5	2	2	3	0	13
Bram [19]	1	5	2	2	2	0	12
Butterman [23]	2	5	1	2	1	0	11
Butterman [22]	2	5	1	2	0	0	10
Buttermann [24]	1	5	1	1	3	0	11
Carragee [26]	1	4	1	2	0	0	8
Carragee [25]	1	5	1	2	2	2	13
Castro [28]	1	5	1	1	0	0	8
Champsaur [29]	1	5	1	2	0	0	9
Chataigner [30]	1	4	1	1	0	0	7
Chung [31]	1	5	2	2	1	2	13
Collins [32]	1	5	1	2	0	0	9
Cvitanic [33]	2	5	2	2	3	2	16
Danchaivijitr [35]	2	5	2	2	4	2	17
Danielsson [36]	1	4	1	2	2	0	10
de Roos [37]	1	5	1	2	1	0	10
Elfering [38]	1	5	2	2	0	2	12
Esposito [39]	2	5	2	2	0	0	11
Frobin [44]	1	5	1	2	2	2	13
Fruhwald [45]	1	4	1	2	0	0	8
Gibson [46]	1	5	2	2	0	0	10
Grand [49]	1	5	2	2	3	0	13
Hajek [52]	1	3	1	2	0	0	7
Ito [61]	1	5	2	2	3	2	15
Jarvik [62]	1	5	2	2	2	1	13
Jevtic [66]	1	5	1	2	0	0	9
Kahn [69]	1	3	2	2	0	0	8
Karchevsky [72]	1	5	2	2	2	2	14
Karppinen [76]	1	4	1	2	3	2	13
Karppinen [74]	1	5	1	2	3	0	12
Karppinen [75]	1	3	1	2	2	2	11
Kato [77]	2	5	1	2	0	0	10
Kerttula [78]	1	5	2	2	3	0	13
Kim [79]	2	3	1	1	3	0	10
Kjaer [81]	2	5	2	2	4	2	17
Kjaer [82]	2	5	1	2	4	2	16
Kleinstuck [83]	1	5	1	2	1	2	12
Kokkonen [84]	2	5	1	2	3	2	15
Korhonen [85]	1	5	1	2	0	0	9
Kuisma [87]	1	5	2	2	4	2	16
Kuisma [88]	1	4	2	2	4	2	15

Table 3 continued

Reference	Study data (0–2)	Descriptive data (0–5)	MRI data (0–2)	VESC definition (0–2)	MRI evaluation (0–4)	Reproducibility (0–2)	Total score per study (0–17)
Lang [89]	1	5	1	2	1	0	10
Lenz [95]	2	5	1	2	0	0	10
Lim [96]	1	5	2	2	3	0	13
Liphofer [98]	2	5	2	2	3	0	14
Lusins [99]	1	3	2	2	0	0	8
Marc [102]	2	5	2	1	2	0	12
Mitra [104]	2	5	2	2	3	0	14
Modic [106]	1	5	2	2	0	0	10
Molla [107]	1	5	2	2	2	1	13
Ohtori [111]	1	5	1	2	2	0	11
Peterson [115]	1	4	2	2	4	2	15
Quack [117]	1	5	2	2	3	2	15
Raininko [118]	1	4	2	2	2	2	13
Rajasekaran [119]	1	3	1	2	1	2	10
Rannou [120]	2	5	1	2	3	0	13
Saifuddin [123]	1	5	2	2	0	0	10
Sandhu [124]	1	3	1	2	2	0	9
Saywell [125]	1	3	1	2	0	0	7
Schenk [126]	1	5	2	2	3	0	13
Schmid [127]	2	5	2	2	2	0	13
Shen [131]	2	5	2	2	2	2	15
Siddiqui [132]	1	5	2	1	2	0	11
Stabler [136]	2	4	2	2	0	0	10
Takeno [138]	2	5	2	1	0	0	10
Toyone [140]	2	4	2	2	2	0	12
Van Goethem [145]	1	3	2	2	0	0	8
Weishaupt [153]	1	5	2	2	3	2	15
Weishaupt [154]	2	5	2	2	3	1	15
Yong [156]	2	5	2	2	3	0	14
Mean quality score ($n = 77$)	1.3	4.6	1.6	1.9	1.6	0.6	11.6

linear pattern, because of the small number of study samples from the non-clinical populations (i.e. non-LBP, general, and working populations). However, when the non-clinical populations were combined in one group, the prevalence of VESC was found to be more than seven times higher among patients with non-specific LBP than in individuals from the non-clinical populations.

As expected, the prevalence of VESC increases with age [87, 106]. This seems plausible as VESC is correlated to disc degeneration [80, 106], which in turn is correlated to age [15].

A statistically higher prevalence of VESC in studies from Europe as compared to studies from Asia was only found for lumbar levels based on 22 studies from Europe and only 2 studies from Asia. Therefore, the difference in the prevalence between the two geographical regions could be explained by an increased awareness of VESC in Europe (i.e. publication bias). Another explanation could be that VESC is more prevalent in Europe, perhaps on the basis of specific genes that are associated with (1) an increased risk of tissue injury, (2) and increased response to injury, or (3) a decreased ability to heal injured tissue. In support of this theory, there are different prevalence rates of genes associated with disc degeneration for individuals from Northern Europe as compared to Asian populations [5, 67, 112, 128, 147]. Also, a recent study suggests that VESC may be related to increased response to injury, as a combination of specific genes (*IL1A* and *MMP-3*) increased the odds of having type 2 changes by eight times [73].

There was a negative association between the prevalence of VESC and the quality score. The overall quality of the study is a proxy for both the technical and analytical

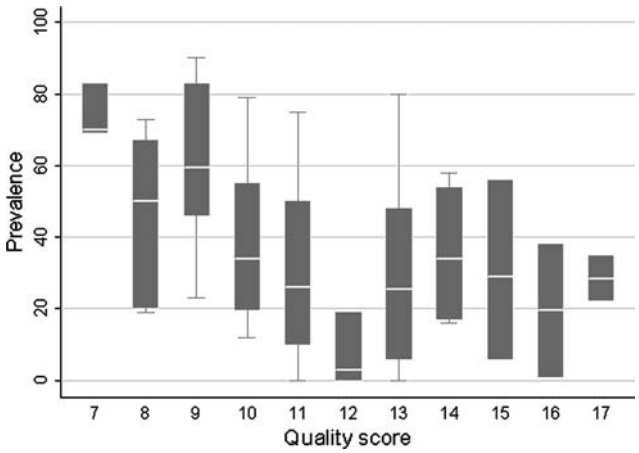

Fig. 8 Median and range of the prevalence rates of vertebral endplate signal changes in relation to the quality score (0–17) from 58 study samples

aspects of the study process. For example, studies that do not have a systematic and reproducible evaluation protocol are more likely to have misclassification and thus more biased estimates of the prevalence.

The reasons why VESC may be painful are not known. The lumbar vertebral endplate contains immunoreactive nerves, as shown in studies of sheep and humans [21, 40], and it has been reported that an increased number of tumour necrosis factor (TNF) immunoreactive nerve cells and fibres are present in endplates that have VESC, especially in type 1 changes [111]. Therefore, the pain may originate from damaged endplates in patients with VESC. Another possibility is that VESC is a proxy for discogenic pain, as VESC is most often seen in relation to disc degeneration [3, 80, 87, 106] and immunoreactive nerves have also been shown to be present in degenerative discs [43]. Interestingly though, the association between VESC and LBP seems to be stronger than that between mere disc degeneration and LBP [80].

The causes of VESC are unknown. Because VESC is present in several specific LBP conditions, there may be several causes. In patients with non-specific LBP, one theory is that disc injury leads to increased loading and shear forces on the endplates, which can lead to fissures of the endplate [2]. In support of this theory, a prospective study of 166 patients with sciatica treated non-surgically, reported a threefold increase of type 1 changes over a period of 14 months [3]. Further evidence in favour of this theory are the results from studies on baboons and rats, where it has been reported that injury to the disc induces changes in the adjacent vertebrae with subsequent bone marrow depletion and degeneration and regeneration of the bone [101, 108, 143].

Systematic literature reviews offer an excellent opportunity to gain an overview of a confusing topic. However, they also have some limitations that need to be addressed. In this review, we sometimes included more than one study sample from the same original study in the analyses [24, 49, 74, 76]. If the original studies are biased in one way or other, this will also be the case for the individual study samples. Thus, the bias of one study will have an unsuitable effect on several study samples.

Another problem is whether the studies submitted to scrutiny had been designed to answer the research questions of the review. In our case, this was true for the prevalence of VESC. Also, the correlation with age had to

Table 4 Odds ratios and 95% confidence intervals of the association between any type of vertebral endplate signal changes and low back pain based on data from ten studies

Study, year	Study sample	LBP outcome	*N*	OR	95% CI
Albert, 2007 [3]	Clinical	Self-reported	166	6.1	2.9; 13.1
Braithwaite, 1998 [18]	Clinical	Discography	152[a]	9.1	2.1; 82.6
Cvitanic, 2000 [33]	Clinical	Self-reported	109	2.4	0.8; 8.1
Ito, 1998 [61]	Clinical	Discography	101[a]	11.6[b]	1.7; ∞
Kokkonen, 2002 [84]	Clinical	Discography	103[a]	1.1	0.5; 2.7
Lim, 2005 [96]	Clinical	Discography	97[a]	0.5	0.1; 1.9
Weishaupt, 2001 [154]	Clinical	Discography	116[a]	19.9[c]	5.2; 109.5
Kjaer, 2005 [81]	General	Self-reported	412	4.2	2.1; 9.2
Kuisma, 2007 [88]	Working	Self-reported	128	2.6[d]	1.5; 3.9
Schenk, 2006 [126]	Working	Self-reported	545[a]	2.0	1.1; 3.6

[a] Number of levels

[b] OR based on median unbiased estimation (see data analysis)

[c] OR calculated from data on all types of Modic changes

[d] Age adjusted OR for LBP pain episodes for all lumbar levels reported in the article

be based on the mean prevalence for each study rather than for specific age groups. Furthermore, a small number of relevant studies make interpretation of data difficult, as in this review, where there were a limited number of studies testing the association with LBP. Finally, there is always the danger of publication bias, particular if the subject is new and perhaps controversial, as is the case with VESC.

The strengths of this review are that the studies included are homogeneous in relation to the definition of VESC, and that VESC is an MRI-finding easy to evaluate and is supported by four studies that have reported the inter-observer reproducibility of a detailed evaluation of VESC with Kappa values ranging from 0.64 to 0.91 [31, 63, 68, 72, 87]. Also, our review was performed by five reviewers and all articles, except those written in German or French ($n = 11$), were evaluated independently by at least two of the reviewers, thus limiting the risk of bias in the evaluation. Finally, the search strategy for this review included articles written in European languages other than English and was made to cover articles that described either the prevalence of VESC or its association with LBP. This broad search strategy would have minimised the risk of missing relevant articles. The strength in relation to the estimation of an association between VESC and LBP is that we used both discography and self-reported LBP as outcomes. This did not only increase the number of studies included in the analysis, but also gave us the opportunity to investigate the association with LBP in non-clinical populations.

Consequences

Our results indicate that clinicians should be aware that patients with "non-specific" LBP may well have a clinically relevant diagnosis. Although we know very little about the treatment and prognosis of VESC, it is possible that giving the patients a likely explanation for their pain could relieve them from anxiety and stress.

In order to improve our knowledge, it is important that researchers report findings in relation to age, sex, ethnicity, and type of LBP. It is relevant to proceed to observational studies of specific subgroups in relation to the aetiology and natural course, also in non-clinical populations.

Conclusion

VESC is a common MRI-finding in patients with non-specific LBP and has been reported to be associated with pain in study samples from the general, working, and clinical populations.

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Appendix

See Table 5.

Table 5

Author, year of publication	
Year of study	
Country of study	
Descriptive	
Population?	Clinical __ General __ Working __
	Others, specify: _____
Patient population if applicable?	LBP __ Sciatica __
	Others, specify: _____
Number of individuals included?	$N =$ _____
Gender ratio	Females, $n =$ _____
	Males, $n =$ _____
Age	Age range _____
	Mean age and SD _____
	Median age and quartiles _____
Race	Asian __ African __ Caucasian __ Not reported __
MRI data	

Table 5 continued

Field strength (Tesla)	Field strength _____ Not reported __			
	Sequence 1	Sequence 2	Sequence 3	Sequence 4
Sequence [e.g. Spin Echo (SE), fast/turbo (FSE/TSE), gradient echo]				
T1/T2/proton density (PD)				
Slice orientation (sag., axial, cor.)				
Repetition time (TR)				
Echo time (TE)				
Flip angle (°)				
Field of view (FOV)				
Matrix (e.g. 256 × 256)				
Slice thickness (mm.)				
Number of acquisitions				
Definition of signal change				
Name of signal changes (e.g. bone marrow oedema, Modic changes)				
Definition of signal changes, including subtypes (e.g. Type 1: hyperintense T2, hypointense T1)				
MRI evaluation				
Number of observers?	N = _____			
Profession of observers? (e.g. neuroradiologist, surgeon)				
Observer blinded to symptoms? (yes/no)	Yes __ No __ Not reported __			
Reproducibility				
Reproducibility? (yes/no)	Yes __ No __			
Intra/inter-tester? (yes/no)	Intra __ Inter __ Not reported __			
Cases/non-cases in reproducibility study? (yes/no)	Cases __ Non-cases __ Not reported __			
Observers blinded to each others readings? (yes/no)	Yes __ No __ Not reported __			
Results? (Kappa, raw data, percentage agreement)				
Main findings?				
Prevalence of signal changes				

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