Systematic Review

Intradiscal Glucocorticoid Injection in Discogenic Back Pain and Influence on Modic Changes: A Systematic Review and Meta-analysis of RCTs

Martin Riegger, MD, PhD[1,2], Huyen Le, MSc[3], Sander M.J. van Kuijk, PhD[3], Gabor Guyenes, MSc[1], Christian Candrian, MD[1,2], Alessandro Cianfoni, MD[4,5], Joshua Hirsch, MD[6], and Eva Koetsier, MD, PhD[2,7]

From: [1]Service of Orthopaedics and Traumatology, Department of Surgery, EOC, Lugano, Switzerland; [2]Faculty of Biomedical Sciences, Università della Svizzera Italiana, Lugano, Switzerland; [3]Department of Clinical Epidemiology and Medical Technology Assessment, Maastricht University Medical Center+, Maastricht, the Netherlands; [4]Diagnostic and Interventional Neuroradiology, Neurocenter of Southern Switzerland EOC; [5]Department of Neuroradiology, Inselspital University Hospital Bern, Switzerland; [6]Department of Radiology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA; [7]Pain Management Center, Neurocenter of Southern Switzerland, EOC, Lugano, Switzerland

Address Correspondence:
Martin Riegger, MD
EOC: Repubblica e Cantone Ticino
Ente Ospedaliero Cantonale
Lugano, Switzerland
E-mail: martin.riegger@eoc.ch

Disclaimer: There was no external funding in the preparation of this manuscript.

Conflict of interest: Each author certifies that he or she, or a member of his or her immediate family, has no commercial association (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted manuscript.

Manuscript received: 12-12-2022
Revised manuscript received: 02-16-2023
Accepted for publication: 03-27-2023

Free full manuscript:
www.painphysicianjournal.com

Background: The benefit of intradiscal glucocorticoid injection (IGI) for discogenic low back pain (LBP) remains controversial.

Objectives: The objective of this study was to systematically assess and meta-analyze the efficacy of IGI compared with these control groups.

Study Design: Systematic review and meta-analysis.

Methods: A comprehensive literature search was performed screening PubMed and Embase through May 2022. Only randomized controlled trials (RCTs) comparing IGI to control groups in adult patients with discogenic lumbar back pain were included. A random effects model was used to pool mean differences of pain intensity (visual analaog scale [VAS] 0-100), and physical function assessed with the Oswestry Disability Index (ODI). Subgroup analyses were stratified by Modic magnetic resonance imaging findings.

Results: Seven studies met inclusion criteria with a total of 626 patients. The short-term (< 3 months) follow-up showed a significant pooled mean difference in both pain intensity (-20.1; 95% CI, -25.5 to -14.7) and physical function (-9.9; 95% CI, -16.1 to -3.6). In the intermediate -term follow-up (3 to < 6 months), only physical function remained significantly better in the glucocorticoid group (-13.1; 95% CI, -22.3 to -3.9). There was no clinically meaningful or significant difference in pain scores and physical function at the long-term (≥ 6 months) follow-up. A subgroup analysis did not demonstrate an effect of Modic (type I) changes on the efficacy of IGI.

Limitations: A limited number of studies was available and consequently publication bias could not be evaluated using a funnel plot. Statistical heterogeneity was detected among the included studies.

Conclusion: We conclude that IGI reduces discogenic LBP intensity and improves physical function effectively at short-term follow-up, and continues to improve physical function at intermediate-term. However, 6 months posttreatment, outcomes are similar in comparison to the control groups. The type of Modic change does not appear to be related with the response to IGI.

Key words: Low back pain, lumbar back pain, intradiscal glucocorticoid injection, modic changes, meta-analysis

Pain Physician 2023: 26:E449-E465

The intervertebral disc is estimated to be the source of chronic low back pain (LBP) in up to 40% of patients (1-4). Discogenic LBP is characterized by persistent axial LBP, associated with degenerative disc disease (DDD) (5-8). Signs of disc degeneration on magnetic resonance imaging (MRI) include the loss of water content, a decreased disc height and endplate subchondral bone changes adjacent to the affected disc, called Modic changes (9,10).

Modic I changes are characterized by subchondral bone edema and inflammation (hypointense signal on MRI T1-weighted imaging [T1WI] and hyperintense signal on T2-weighted imaging [T2WI]). Modic II changes are characterized by fatty degeneration (hyperintense signal on T1WI and isointense or slightly hyperintense signal on T2WI) though the appearance of fat can vary based on the underlying T2-weighted sequence (9,10). Modic III changes are characterized by subchondral sclerotic bone formation (hypointense signal on T1WI and T2WI) (9,10). Modic I-associated LBP has specific clinical and biological features, including an inflammatory pain pattern (11), elevated high-sensitivity C-reactive protein serum values (12), and local inflammation (13). Studies have suggested that Modic I changes are associated with LBP (14-17).

Conservative management of discogenic pain includes anti-inflammatory drugs, physiotherapy, and multidisciplinary biopsychosocial rehabilitation (18). If conservative treatment fails, minimally invasive treatments may be considered. The evidence of efficacy for most minimally invasive treatments for discogenic LBP, like intradiscal mesenchymal stem cells and platelet-rich plasma injection and intradiscal radiofrequency treatment, is low (19-21). Alternatives such as antibiotic treatment for patients with discogenic pain are still in the experimental phase. Percutaneous discectomy, while well studied, is beyond the scope of this review, as it is generally more effective in neuropathic radicular pain than in LBP without radicular pain (22).

The inflammatory aspect of Modic I changes provides a rationale for evaluating treatments targeting local inflammation, such as epidural or intradiscal glucocorticoid injection (IGI). Randomized controlled trials (RCTs) on the efficacy of IGI versus control have been limited by their low statistical power due to small sample sizes (23,24). Therefore, the aim of this review is to systematically assess and meta-analyze the efficacy of IGI compared with these controls. Parameters studied include pain intensity, physical function improvements, quality of life, and analgesics treatments in patients with discogenic LBP. These patients' discogenic LBP diagnosis was determined by a combination of medical history, clinical examination, and MRI scan. In addition, we assessed the possible correlation of Modic changes with the efficacy of IGI in comparison to control groups.

Methods

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) (25,26). The study was registered a priori on the International Prospective Register of Systematic Reviews (PROSPERO CRD42022341785). We do not have any deviations from the protocol to report.

Search Strategy

We searched on PubMed and Embase for randomized, controlled trials of IGI versus control (insertion of a needle into the intervertebral disc with or without injection of contrast dye [discography], saline, anesthetics, or supposedly inactive agents). Three authors (MR, EK, and HL) independently performed a comprehensive literature search of PubMed and Embase to find relevant peer-reviewed articles published from their inception through May 2, 2022. No language restrictions were applied. The search string included keywords related to LBP, intradiscal injection, and RCTs. Detailed search strings are shown in Appendix A. To expand the literature search, the references of the eligible articles and reviews with related topics were also screened for possible additional records.

Study Selection

Three reviewers (MR, EK and HL) independently selected studies based on predefined criteria:

1) Studies — only RCTs were considered eligible

2) Patients — all studies in adults with LBP related to DDD as diagnosed by a combination of clinical examination and MRI scan were eligible, regardless of pain duration and intensity; studies assessing effectiveness on radicular pain as the primary outcome and studies in adults with LBP related to facet joint disease were excluded; no age restrictions were applied

3) Interventions — studies that compared IGI at any dose with any control treatment (e.g., insertion of a needle into the intervertebral disc with or without injection of contrast dye [discography], saline, anesthetics, or supposedly inactive agents) were eligible

4) Outcome measures — The primary outcome was

pain intensity quantified either as continuous value, measured by the Numeric Rating Scale (NRS-11) or Visual Analog Scale (VAS), or as the number of patients reporting pain improvement after receiving treatments; the secondary outcome measures were improvement in physical function, quality of life, analgesic usage, and adverse events (AEs) and serious adverse events (SAEs). Physical function was measured by the Oswestry Disability Questionnaire (ODI) or the Quebec Back Pain Disability Scale (QBPDS). Quality of life was assessed by the short form (SF)-36 or SF-12 questionnaires. Analgesic usage was recorded as the number of patients using analgesic treatments during follow-up; the definition of analgesic drugs depended on each individual study. AEs and SAEs were recorded as the number of patients experiencing one or more among the total sample or just as the number of reported cases, whichever the eligible study reported.

The studies were first manually screened based on the title and abstract by the 3 independent reviewers. Studies passing this process were assessed in full text. Any disagreement among the 3 reviewers was addressed by discussion.

Data Extraction

Three reviewers (MR, EK, and HL) independently extracted the data according to a standardized form. For each selected article, the following information was collected: title, first author, published year, country, patient characteristics, study design, sample size, inclusion and exclusion criteria, type of glucocorticoid and doses, type of control and doses, measurement scale, follow-up time, and, at each available time point, the pain intensity, functional status and quality of life scores, or change scores, (expressed as mean or median, with either SD, SE, CI, or Inter Quartile Range (IQR). The number of patients reporting improved symptoms was based upon the definition used by the authors, as well as the number of patients using analgesic drugs (time point and sample size), the number of patients experiencing AEs and SAEs (time point and sample size). Any discrepancy was solved through discussion.

For studies with insufficient information, we searched for more information on the ClinicalTrials.gov platform or attempted contact with the corresponding author up to 3 times. For studies representing results in graphs only, and without a response from the corresponding author, WebPlotDigitizer (Version 4.5) was used to extract the mean and CI (tool available at https://automeris.io/WebPlotDigitizer/) (27).

Quality Assessment

The quality of the included studies was critically appraised using the second version of the Cochrane risk-of-bias tool for randomized trials by one reviewer and then discussed in a conference call of 4 reviewers (GG, MR, EK, and HL) (28). In short, the Cochrane risk-of-bias tool for randomized trials focuses on 5 domains. They are the randomization process, intervention, missing outcome data, measuring outcomes, and reporting outcomes. Conflict was resolved through consensus. The overall risk of bias was concluded based on each of the 5 domains.

Statistical Analysis

The mean difference (95% CI) for the continuous outcomes and the risk ratio (RR) and 95% CI for dichotomous outcomes was calculated to compare between the glucocorticoid and control groups. The inverse-variance random-effects model was used to pool the data across studies, and the results were presented in Forest plots. Pain scores measured on an 11-point NRS were converted to the 0 (no pain) - 100 (maximum pain) VAS scale before pooling; a decrease of 20 units in pain score was considered to be of minimal clinical importance (29). Results from studies measuring physical function as an ODI score (0-100, a lower score means less disability) were pooled. A decrease of at least 10 points in ODI was considered to be clinically important (29). Differences in postintervention scores were pooled. In case no postintervention scores were available, we used the difference in change-from-baseline score.

Unreported SDs were calculated from 95% CI/90% CI as recommended by the Cochrane collaboration (30) and from IQR based on Wan et al for data with skewed distribution (31).

Quality of life was measured in only 2 studies utilizing 2 different questionnaires, making it unsuitable for meta-analysis and thus quality of life findings were described in narrative form. For dichotomous outcomes, numbers of patients experiencing the event and sample sizes of the groups were used to calculate the RR between both groups. AEs and SAEs were reported in only 2 studies. However, the available data were heterogeneous in their way of reporting; therefore, we chose to describe it in narrative form without meta-analysis. We separated outcomes for 3 time points: short-term (< 3 months), intermediate-term (3 – < 6 months) and long-term (≥ 6 months).

For studies reporting multiple outcomes within

each time category, data of the longest time point were chosen for pooling and data of the other time points were described in a descriptive table. First, results for the overall sample regardless of their type of Modic changes were pooled, then a subgroup analysis including only results from patients with Modic I was performed. For studies reporting results separately for different kinds of Modic changes, we combined those into an overall estimate according to the Cochrane handbook for systematic reviews of intervention studies (30).

Between-study heterogeneity was evaluated based on the Cochrane χ^2 test and I^2, where $P > 0.1$ and $I^2 > 50\%$ were considered a sign of significant heterogeneity. A funnel plot was planned to determine the risk of publication bias, but the small number of studies inhibited that. The meta-analysis was conducted using the packages "meta" and "metafor" in R version 4.1.2 (The R Foundation).

Results

Literature Search

Literature search results are summarized in Fig. 1 and briefly described below.

Overall, 84 potential records were identified from the comprehensive literature search. After a thorough screening process, 7 articles were included in the qualitative analysis (systematic review) and in the quantitative analysis (meta-analysis) (Fig. 1) (23,24,32-36). The characteristics and technical aspects of the 7 included studies in the systematic review are presented in Table 1. The main findings are listed in Table 2.

Qualitative Analysis (Systematic Review)

Study Characteristics

Table 1 shows the characteristics of eligible studies. All selected articles were RCTs published from 1992 through 2021 by research groups from differ-

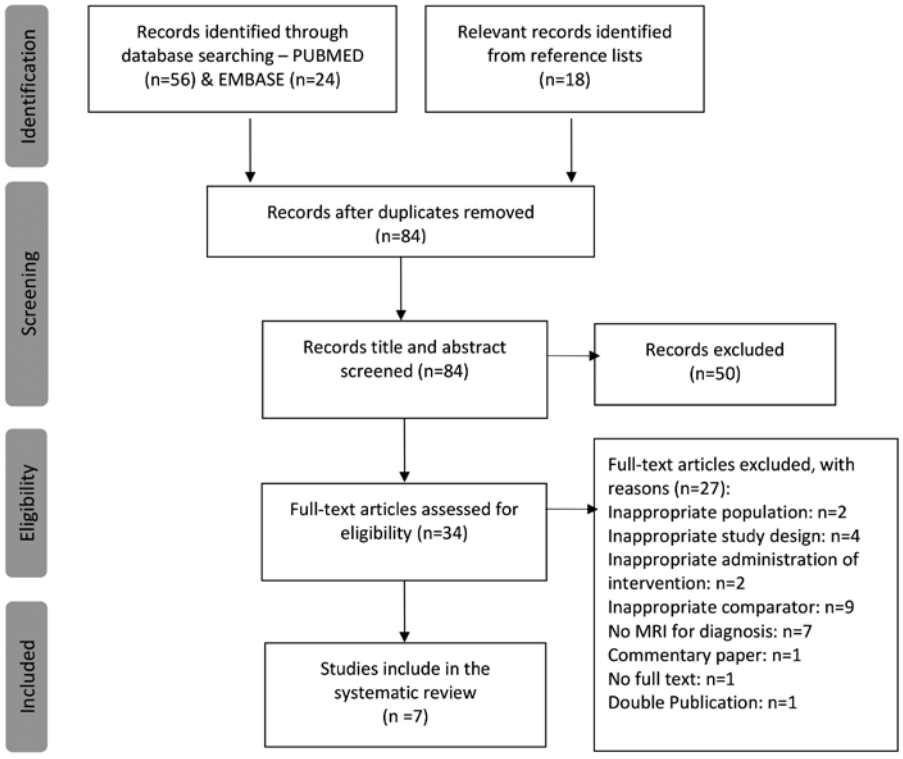

Fig. 1. *Study selection flowchart.*

Table 1. Characteristics of included studies.

Study, year	Country	Study design	Partici-pants	Glucocor-ticoid	Control	Modic Classifi-cation	N Gluco-corticoid	N Control	Follow-up (months)	Measurement					Adverse events
										Pain inten-sity	Pain improve-ment	Physical func-tion	Quality of life	Anal-gesic treat-ment	
Simmons et al (35), 1992	USA	Double-blinded RCT	One-level symptomatic disc disease	Methyl prednisolone	Bupivacaine	NR	n = 14	n = 11	10-14 [days]	VAS	Patient-reported	ODI	No	No	No
Buttermann et al (32), 2004	USA	Non-blinded RCT	Chronic discogenic LBP	Beta-methasone & Discography	Discography	Modic I	n = 40	n = 38	1-3; 4-6;7-12; 12-24	VAS	Patient-reported	ODI	No	Yes[a]	No
						Not modic I	n = 46	n = 47							
Khot et al (34), 2004	UK	Single-blinded RCT	Chronic discogenic LBP	Methyl prednisolone	Saline	NR	n = 60	n = 60	12	VAS	No	ODI	No	No	No
Cao et al (33), 2011	China	Double-blinded RCT	Chronic discogenic LBP	Beta-methasone	Saline	Modic I[b]	n = 20	n = 20	3,6	VAS	No	ODI	No	No	No
						Modic II[c]	n = 20	n = 20							
Yu et al (36), 2012	China	Double-blinded RCT	Chronic discogenic LBP with negative discography	Dexametha-sone & Dis-cography	Saline	NR	n = 23	n = 22	1-6	VAS	No	ODI	No	No	No
Nguyen et al (23), 2017	France	Double-blinded RCT	Chronic LBP with active discopathy	Prednisolone & Iodixanol contrast	Iodixanol contrast	Modic I	n = 67	n = 68	1,12	NRS	Yes[d]	QBPDS	SF-12	Yes[e]	Yes
Tavares et al (24), 2020	France	Single-blinded RCT	Chronic LBP with active discopathy	Prednisolone	Lidocaine	Modic I	n = 24	n = 26	1,3,6	VAS	No	ODI	SF-36	Yes[e]	Yes

RCT, Randomized controlled trial; NR, nonreport; VAS, visual analog scale; ODI, oswestry disability index; LBP, low back pain; QBPDS, Quebec back pain disability scale; SF-12, short-form 12 questionnaire; SF-36, short-form 36 questionnaire; NRS, numeric rating scale.

[a]compare pain medication usage after injection versus before (much more, more, same, less, much less); [b]Modic I group included Modic change Type I and Type I–predominated mixed Type I/II; [c]Modic II group included Modic change Type II and Type II–predominated mixed Type I/II; [d]Pain improvement was defined when the NRS intensity was lower than 40 (one of the inclusion criteria was that the NRS was higher than 40); [e]Use of analgesics and NSAIDs (yes/no).

Table 2. *Main findings*.

Study, year	Modic types	Findings					
		Pain score[a]	Pain improvement[b]	Physical function[c]	Quality of life	Analgesic treatment	Adverse events
Simmons et al (35), 1992	Overall	Day 10-14[f] G group: 43% less pain C group: 36% less pain	Day 10-14 G group: 21% C group: 9%	Day 10-14 day[f] G group: 36% improved C group: 27% improved	N/A	N/A	N/A
Buttermann et al (32), 2004	Modic type I[d]	Month 1-3 G group: 42.1 (28.9) C group: 71.9 (14.3) Month 4-6 G group: 43.1 (30.7) C group: 70.1 (16.2) Month 7-12 G group: 46.2 (34.9) C group: 67.0 (4.0) Month 12-24 G group: 46.1 (28.0) C group: e	Month 1-3 G group: 68% C group: 0% Month 4-6 G group: 50% C group: 0% Month 7-12 G group: 33% C group: 0% Month 12-24 G group: 25% C group: 0%	Month 1-3 G group: 39.2 (24.5) C group: 53.5 (20.8) Month 4-6 G group: 32.9 (25.8) C group: 50.6 (19.5) Month 7-12 G group: 31.3 (23.7) C group:e Month 12-24 G group: 27.8 (24.9) C group:e	N/A	Compared with pain medication use before injectionf G group: 2.5% used more 55.0% used same 37.5% used less 5.0% used much less C group: 10.5% used more 89.5% used the same	N/A
	Not Modic type I[d]	Month 1-3 G group: 67.0 (20.5) C group: 74.9 (12.1) Month 4-6 G group: 61.1 (16.9) C group: 75.0 (20.7) Month 7-12 G group: 65.2 (30.5) C group: 76.0 (23.8) Month 12-24 G group: 65.2 (30.5) C group: 68.2 (23.2)	Month 1-3 G group: 17% C group: 0% Month 4-6 G group: 17% C group: 0% Month 7-12 G group: 13% C group: 0% Month 12-24 G group: 11% C group: 2%	Month 1-3 G group: 53.0 (19.8) C group: 54.9 (18.3) Month 4-6 G group: 54.4 (23.8) C group: 49.2 (26.1) Month 7-12 G group: 54.8 (28.1) C group: 56.4 (23.1) Month 12-24 G group: 53.4 (24.6) C group: 51.0 (14.1)	N/A	Compared with pain medication use before injectiong G group: 2.2% used more 93.5% used the same 2.2% used less 2.1% used much less C group: 4.1% used more 93.9% used the same 2.0% used less.	N/A
Khot et al (34), 2004	Overall	Month 12[h] G group: -2.5 (9.6) C group: 0.0 (15.2)	N/A	Month 12[i] G group: -2.3 (16.9) C group: -3.4 (12.9)	N/A	N/A	N/A

Table 2 (cont). *Main findings*.

Study, year	Modic types	Findings					
		Pain score[a]	Pain improvement[b]	Physical function[c]	Quality of life	Analgesic treatment	Adverse events
Cao et al (33),2011	Modic I[k]	Month 3 G group: 18.0 (10.3) C group: 70.0 (13.3) Month 6 G group: 23.0 (9.5) C group: 75.0 (10.8)	N/A	Month 3 G group: 13.1 (2.2) C group: 42.0 (13.9) Month 6 G group:14.7 (3.2) C group: 44.4 (14.0)	N/A	N/A	N/A
	Modic II[l]	Month 3 G group: 16.0 (8.4) C group: 68.0 (10.3) Month 6 G group: 21.0 (9.9) C group: 64.0 (10.7)	N/A	Month 3 G group: 12.7(2.1) C group:33.3(10.6) Month 6 G group: 13.8(2.3) C group:33.8(12.0)	N/A	N/A	N/A
Yu et al (36),2012	Overall	Week 1 G group: 38.4(13.9) C group: 65.0(9.1) Week 4 G group: 42.8(14.0) C group: 67.2(4.3) Week 12 G group: 55.0(10.0) C group: 69.0(4.3) Week 24 G group: 63.9(15.4) C group: 66.7(5.8)	N/A	Week 1 G group: 25.4(6.7) C group: 48.8(5.4) Week 4 G group: 32.1(7.9) C group: 46.7(4.9) Week 12 G group: 40.9(8.8) C group: 53.0(8.0) Week 24 G group: 49.2(9.5) C group: 51.0 (7.1)	N/A	N/A	N/A
Nguyen et al (23), 2017	Modic I	Month 1[m] G group: 36.5(22.8) C group: 50.3(24.7) Month 3[m] G group: 50.5(26.1) C group: 43.9(26.1) Month 6[m] G group: 54.4(23.6) C group:42.0(25.0) Month 12[m] G group:51.5(24.1) C group:42.5(24.0)	Month 1[n] G group: 55.4% C group: 33.3%	Month 1[o] G group: -11.9 (16.0) C group: -6.7 (15.9) Month 12[o] G group: -6.9(18.2) C group: -7.6(17.9)	Physical component[p] Month 1 G group:5.8 (8.9) C group:4.5 (8.8) Month 12 G group: 3.9 (8.3) C group: 6.9 (8.3) Mental component[p] Month 1 G group: 5.4 (9.6) C group: 5.0 (9.6) Month 12 G group 2.9 (11.3) C group 4.5 (11.1)	Month 1[q] G group: 22.2% C group: 30.2% Month 12[q] G group: 33.3% C group: 50.9%	Over 12 months: ≥1 AEs: G group: 97% C group: 94.1% ≥1 SAEs: G group: 43.3% C group: 39.7%

Table 2 (cont). *Main findings*.

Study, year	Modic types	Findings					
		Pain score[a]	Pain improvement[b]	Physical function[c]	Quality of life	Analgesic treatment	Adverse events
Tavares et al.(24), 2020[r]	Modic I	Month 1 G group: 38.4 (29.1) C group: 65.6 (18.6) Month 3 G group: 44.7 (29.4) C group: 53.4 (24.9) Month 6 G group: 44.4 (27.7) C group: 47.3 (21.2)	N/A	Month 1 G group: 33 (16) C group: 37 (14) Month 3 G group: 30 (14) C group: 36 (13) Month 6 G group: 29 (18) C group: 34 (17)	Physical components Month 1 G group: 37.3(9.6) C group: 31.9 (6.6) Month 3 G group: 38.1(9.4) C group: 35.8(7.4) Month 6 G group: 42.0 (9.5) C group: 37.8 (7.2) Mental components Month 1 G group: 43.1(12.4) C group: 41.8(10.5) Month 3 G group: 44.6(13.8) C group: 42.3(9.9) Month 6 G group: 43.8(10.5) C group: 42.1(10.8)	Antalgics usaget Month 1 G group: 60% C group: 57% NSAIDs usageu Month 1 G group: 15% C group: 19%	Over 6 months: SAEs[v]: G group: 3 cases C group: 4 cases.

G group, glucocorticoid group; C group, control group; AEs, adverse events; SAEs, serious adverse events.

[a]All studies quantified pain intensity on the VAS except for the study by Nguyen et al., where pain intensity was measured in NRS. Pain intensity in VAS was transferred to a 0-100 scale. Pain intensity was presented as mean and SD except for where stated; [b]Results were presented in percentages of pain improvement in each group; [c] Physical function was measured in ODI except for the study by Nguyen et al., where the physical function was measured in QBPDS. Physical function was presented as mean and SD except for where stated; [d]Upper and lower 95%CI of pain intensity and physical function were extracted from figures, and mean(SD) was calculated from this; [e]No information as the 95%CI beyond the figures' boundaries and we cannot extract this information; [f]Glucocorticoid group: first 3-month follow-up period; Control group: not stated specific time; [g]The specific time was not reported for both the Glucocorticoid group & Control group; [h]Pain intensity was represented as mean change (SD), which was calculated from median change (IQR); [i]Physical function was represented as mean change (SD) based on study report; [k]Modic I group included Modic change Type I and Type I–predominated mixed Type I/II; [l]Modic II group included Modic change Type II and Type II–predominated mixed Type I/II; [m]Pain intensity was measured in NRS. Results were represented in mean (SD), which was calculated from the mean (95%CI); [n]percentage of patients with pain intensity < 40 (NRS 0-100) (one of the inclusion criteria was that the NRS was higher than 40); [o]physical function was measured in QBPDS. Results were represented as mean change (SD), which was calculated from mean change (95%CI); [p]Quality of life was measured in SF-12. Results were represented as mean change (SD), which was calculated from mean change (95%CI); [q]Percentage of patients who used analgesics and NSAIDs; [r]Information about pain intensity, physical function and quality of life were collected from contacting the authors; [s]Quality of life was measured in SF-36 and presented as mean (SD); [t]Percentage of patients who used analgesics; [u]Percentage of patients who used NSAIDs. [v]Could not be determined whether these events happened in different patients or in the same patients from the data reported.

ent continents (North America, Asia and Europe). The patients in both the glucocorticoid group (314) and the control group (312) had chronic LBP due to a degenerative disc disease without any other spinal pathologies. The mean group size was 35 (14 – 67) patients in the glucocorticoid group and 35 (11 – 68) in the control group.

In 4 of the 7 included studies, the Modic classification was used. In all 4 studies using the Modic classification, subgroup analyses were performed comparing the overall result with the results in the Modic type I group. However, only one study distinguished between Modic type I and type II in its subgroup analyses. Four different kinds of glucocorticoids were used in the individual studies. Methylprednisolone, betamethasone, and prednisolone acetate were all used in 2 studies; dexamethasone was used in one. The studies used different agents in their control groups. Three studies used a saline solution, 2 used a local anesthetic (lidocaine, bupivacaine), and 2 used contrast dye.

Follow-up was reported in 3 periods: short-term (one week to less than 3 months) in 5 studies, intermediate-term (3 to less than 6 months) in 4 studies, and long-term (6 to 24 months) in 6 studies. The measurements consisted of pain scores (6 studies used VAS, one study used NRS-11), pain improvement (3 studies), physical function (6 studies used ODI, one study used QBPDS), quality of life (2 studies),analgesic treatment (3 studies) and adverse events (2 studies).

Main Findings

Short-term pain intensity scores were reported in 4 studies. The glucocorticoid group showed statistically significant better results compared to the control group in pain intensity and ODI. The glucocorticoid group showed better results compared to the control group at the intermediate-term follow-up for ODI. ODI was reported in 4 studies, while pain scores were reported in 5 studies. Mean pain intensity was lower in the glucocorticoid group compared to the control group. However, Nguyen et al reported higher pain intensity in the intermediate-term follow-up in the glucocorticoid group (50.5 glucocorticoid vs 43.9 control) which was not statistically significant (23). The mean ODI scores in the glucocorticoid group were generally lower than in the control group, except for the "not-Modic I" subgroup of Buttermann et al (32). In this group, the mean ODI was slightly higher in the glucocorticoid group (54.4 glucocorticoid vs 49.2 control) but with no statistical significance (32).

Long-term pain intensity was reported by 6 studies and 4 studies reported ODI scores. Mean pain intensity was lower in the glucocorticoid group in all 6 reporting studies, but the difference was less pronounced compared to the short- and intermediate-term follow-up. Similar findings were observed in the ODI analysis.

Quality of life was measured in 2 studies at months one, 3, 6 and 12 using SF-12 and SF-36 (23,24). Overall, at months one, 3 and 6, patients in the glucocorticoid group had a higher score for quality of life than the control group in both physical and mental aspects (23,24). However, at month 12, physical and mental health-related quality of life was lower in the glucocorticoid group (23).

There were 3 studies assessing analgesic treatments between the 2 groups. One study compared medication usage pre- and postinjection and 2 studies recorded postinjection medication usage (23,24,32). Compared to preinjection analgesic usage, at postinjection a low number of patients in the glucocorticoid group used more pain medications and a higher number of them used less or much less pain medications than the control groups (32). Nguyen et al (23) found that at months one and 12, the proportion of patients who used analgesics and nonsteroidal anti-inflammatory drugs in the glucocorticoid group was lower than the control group. Meanwhile, Tavares et al (24) demonstrated that at one month, compared to the control group, a higher percentage of patients in the glucocorticoid group used analgesic medication, but a lower percentage of them used nonsteroidal anti-inflammatory drugs, although the differences were slight.

Two studies reported the occurrence of AEs and SAEs (23,24). Nguyen et al (23) reported that at their 12-month follow-up, a slightly higher percentage of patients in the glucocorticoid group experienced at least one AE or SAE compared to the control group. Of note, within reported SAEs, no patients in the glucocorticoid group and only one patient in the control group were possibly related to the intervention (i.e., an increase in radicular leg pain in the 24 hours postinjection) (23). Over a 6 month period, Tavares et al (24) recorded 3 SAEs in the glucocorticoid group and 4 SAEs in the control group; however, we lacked information about the denominator to calculate the percentage. No spondylodiscitis or intervertebral disc calcifications were reported in the included studies.

Quality Assessment

The quality assessment results are shown in Fig.

2. Most of the studies showed overall concerns after assessing the above-mentioned domains (23,24,32-36). These overall concerns were mainly caused by incomplete reporting of the study method and results. The measurement of the outcomes was appropriate for most studies, although "incompletion in reporting the possible measurement" or "ascertainment differences" between intervention groups caused the main concerns (23,24,32-36). In study by Butterman et al (32) there was a high risk of difference in measurement between groups. The domain less susceptible to bias was the description of the randomization process. In most of the studies the randomization and allocation concealment were ensured (23,24,33-36). Blinding was another source of concern; most of the studies assured that patients were not aware of their intervention (23,24,33-36), although the blinding of providers was only applied in some of the studies (33,35,36).

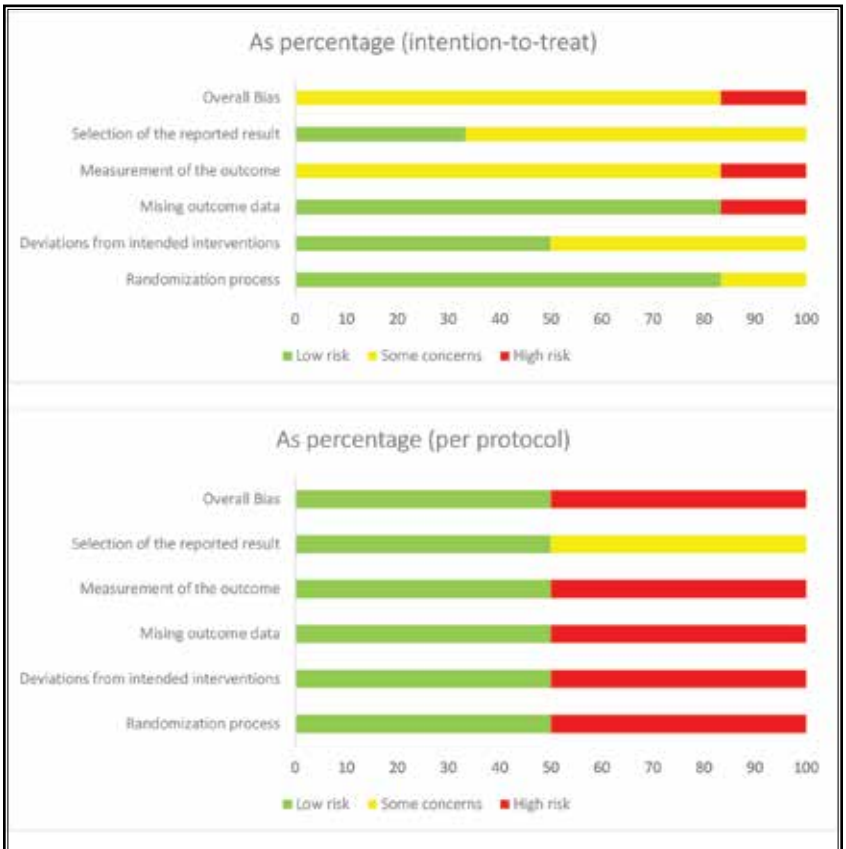

Fig. 2. *The quality assessment of the included studies according to the Cochrane risk-of-bias tool for randomized trials tool. The risk of bias is colored. Green: "low" risk of bias, yellow: "some" risk of bias and red: "high" risk of bias.*

Quantitative Analysis (Meta-analysis)

All 7 studies from the qualitative analysis, including 626 patients (314 glucocorticoid group, 312 control group), were selected for the meta-analysis. Results of the meta-analyses are shown in Figs. 3–9. Meta-analyses were performed for short-term, intermediate-term and long-term follow-up regarding pain intensity scores (0-100), ODI (0-100), Modic type I if possible, with subgroup-analyses. For short-term follow-up it was possible to perform a meta-analysis for pain improvement.

Meta-analyses of the Short-Term Follow-up:

The short-term follow-up for the pain intensity scores (Fig. 3) showed a pooled mean difference of -20.1 (95% CI; -25.5 to -14.8), in favor of the glucocorticoid group. Heterogeneity was low with I^2 = 35%. Regarding pain intensity scores for Modic type I, the subgroup analysis was similar: the pooled mean difference was -22.8 (95% CI, -33.7 to -12.0). Moderate heterogeneity was detected (I^2 = 64%). On the ODI (Fig. 4), the pooled mean difference was -9.9 (95% CI, -16.1 to -3.6). Heterogeneity was moderate at I^2 = 67%.

The pooled mean difference in the subgroup analysis for Modic type I was reported in 2 studies. The pooled mean difference was -9.08 (95% CI, -19.2 to 1.0) A low heterogeneity was detected (I^2 = 52%). In the short-term follow-up, they were lower on average in the glucocorticoid group versus the control group (23,24,32,36). The subgroup analysis of Modic type I was similar to the overall analysis. Pain improvement was only available for short-term follow-up and was measured by 3 studies (23,32,35). A meta-analysis for pain improvement was only available for short-term follow-up. Since a subgroup analysis for Modic type I was investigated in only 2 studies, it was considered as insufficient data for meta-analysis. The results of the meta-analysis for pain improvement are shown in Fig. 5. The pooled value in the 2 groups (n = 165/n = 169) was 4.68 (95% CI, 0.6 to 36.5). Heterogeneity was moderate (I^2 = 71%).

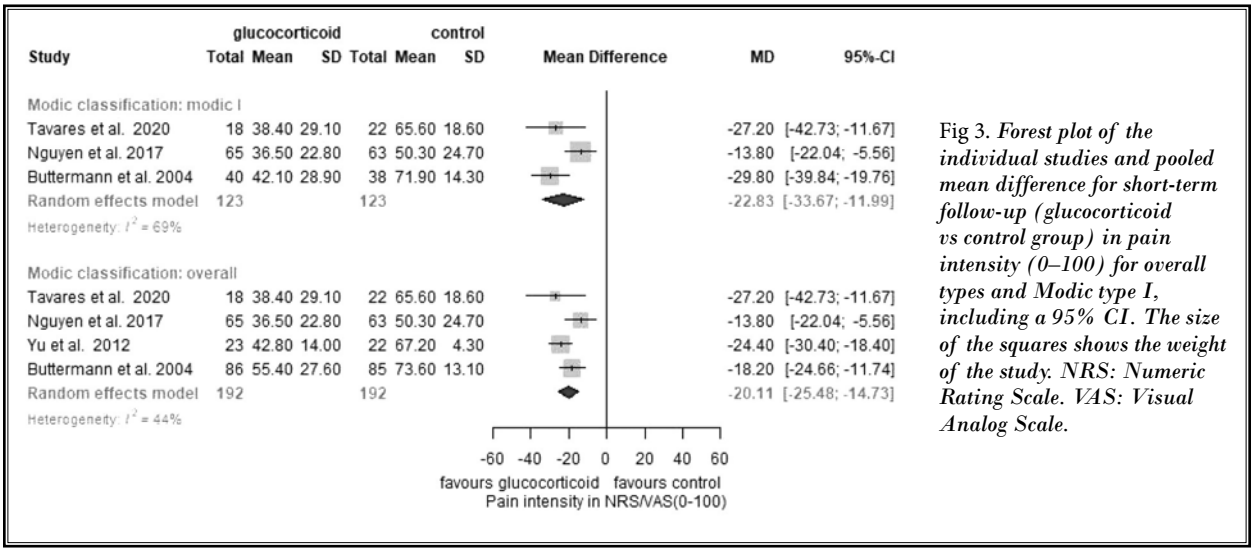

Fig 3. *Forest plot of the individual studies and pooled mean difference for short-term follow-up (glucocorticoid vs control group) in pain intensity (0–100) for overall types and Modic type I, including a 95% CI. The size of the squares shows the weight of the study. NRS: Numeric Rating Scale. VAS: Visual Analog Scale.*

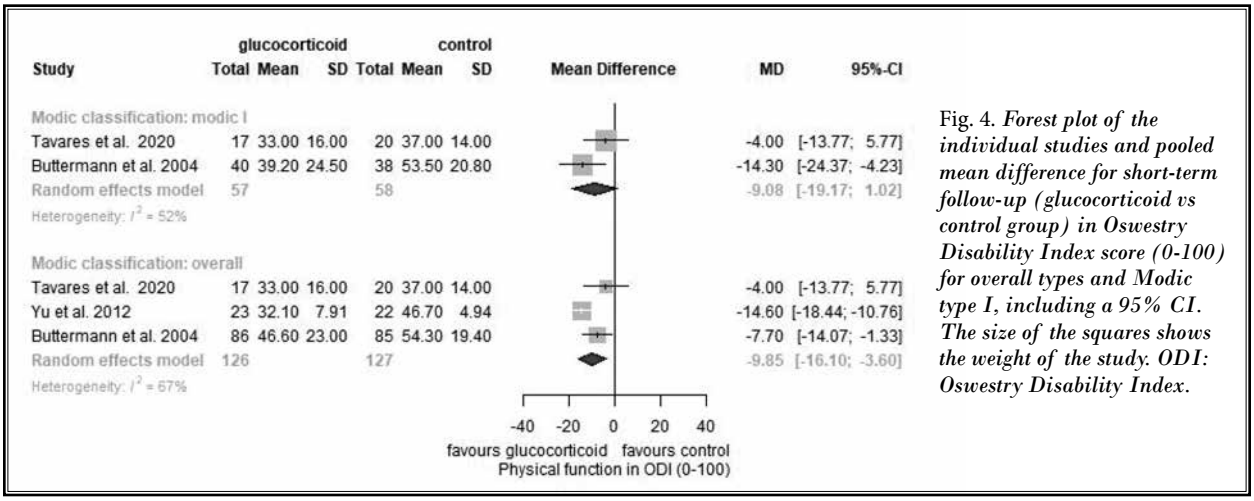

Fig. 4. *Forest plot of the individual studies and pooled mean difference for short-term follow-up (glucocorticoid vs control group) in Oswestry Disability Index score (0-100) for overall types and Modic type I, including a 95% CI. The size of the squares shows the weight of the study. ODI: Oswestry Disability Index.*

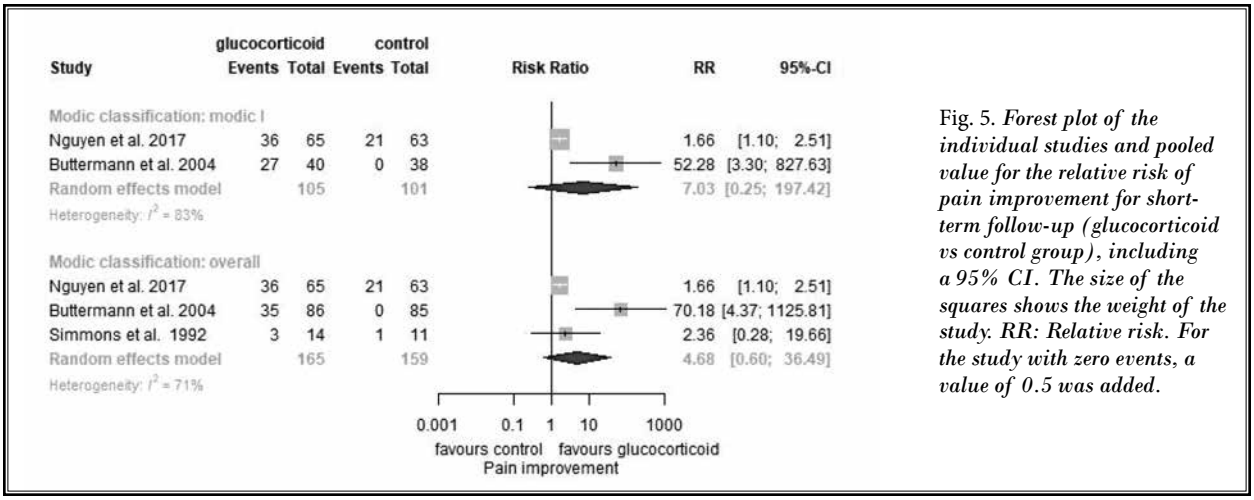

Fig. 5. *Forest plot of the individual studies and pooled value for the relative risk of pain improvement for short-term follow-up (glucocorticoid vs control group), including a 95% CI. The size of the squares shows the weight of the study. RR: Relative risk. For the study with zero events, a value of 0.5 was added.*

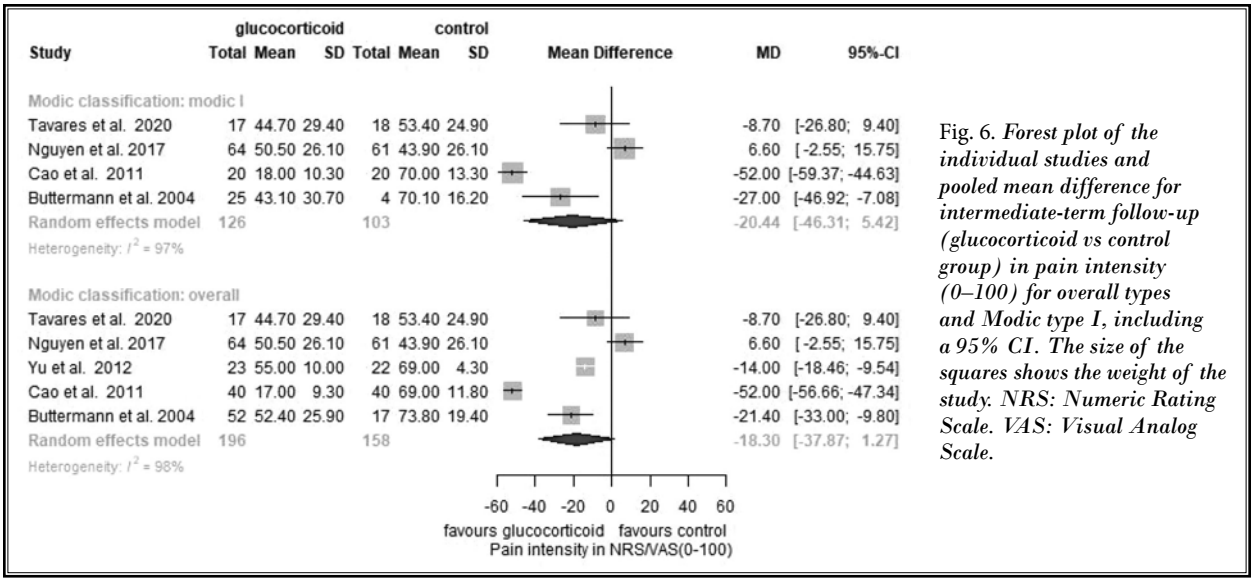

Fig. 6. *Forest plot of the individual studies and pooled mean difference for intermediate-term follow-up (glucocorticoid vs control group) in pain intensity (0–100) for overall types and Modic type I, including a 95% CI. The size of the squares shows the weight of the study. NRS: Numeric Rating Scale. VAS: Visual Analog Scale.*

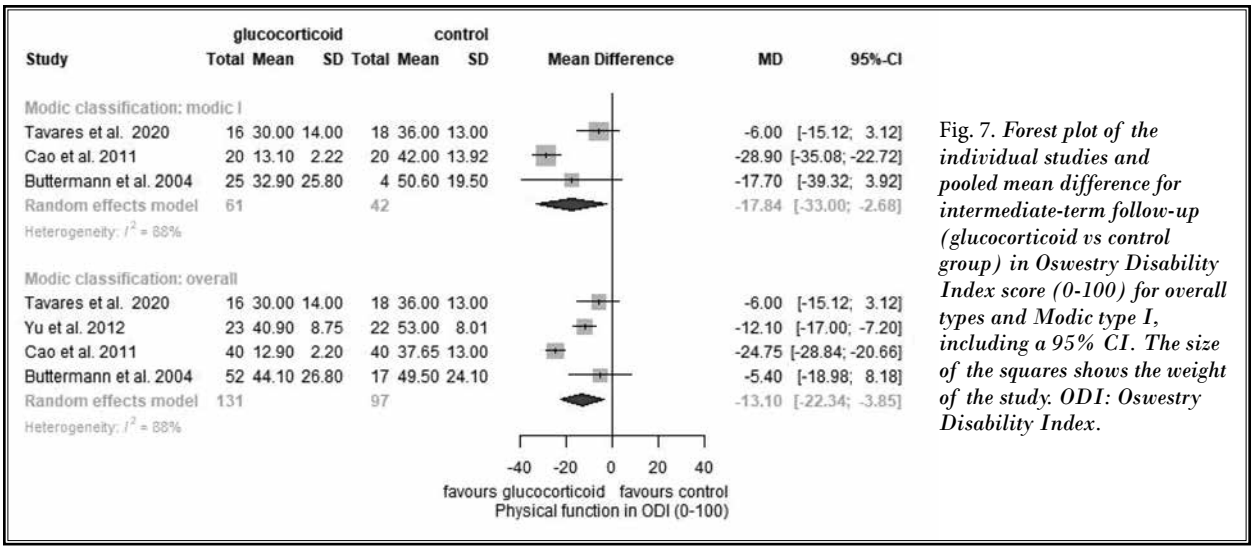

Fig. 7. *Forest plot of the individual studies and pooled mean difference for intermediate-term follow-up (glucocorticoid vs control group) in Oswestry Disability Index score (0-100) for overall types and Modic type I, including a 95% CI. The size of the squares shows the weight of the study. ODI: Oswestry Disability Index.*

Meta-analyses of the Intermediate-Term Follow-Up:

The intermediate-term pain intensity and ODI are shown in Figures 6 and 7, respectively. The pain intensity scores showed a pooled mean difference of -18.3 (95% CI: -37.9; 1.3) with heterogeneity of I^2 = 98%. In the subgroup analysis for Modic type I, the pooled mean difference was -20.4 (95%CI: -46.3; 5.4). Heterogeneity was I^2 = 97%. The quantitative analysis of the ODI in the overall studies resulted with a pooled mean difference of -13.1 (95%CI: -22.3; -3.9). For the Modic type I subgroup analysis, the pooled mean difference was -17.8 (95%CI: -33; -2.7), with heterogeneity of I^2 = 88%.

Meta-analyses of the Long-Term Follow-up:

The quantitative analyses for pain intensity scores and ODI at long-term follow-up are shown in Figures 8 and 9. The pooled mean difference of pain intensity score was -11.2 (95%CI: -27.9; 5.6)(I^2 = 98%). In the subgroup analysis for Modic type I, the pooled mean difference for pain intensity score (glucocorticoid vs control) was -17.0 (95%CI: -43.8; 9.9) (I^2 = 98%). Overall results for the ODI showed a pooled mean difference of -7.8 (95%CI: -19.9; 4.2) (I^2 = 96%). In the subgroup Modic type 1, the pooled mean difference was -17.9 (95%CI: -42.1; 6.3). Heterogeneity was I^2 = 92%.

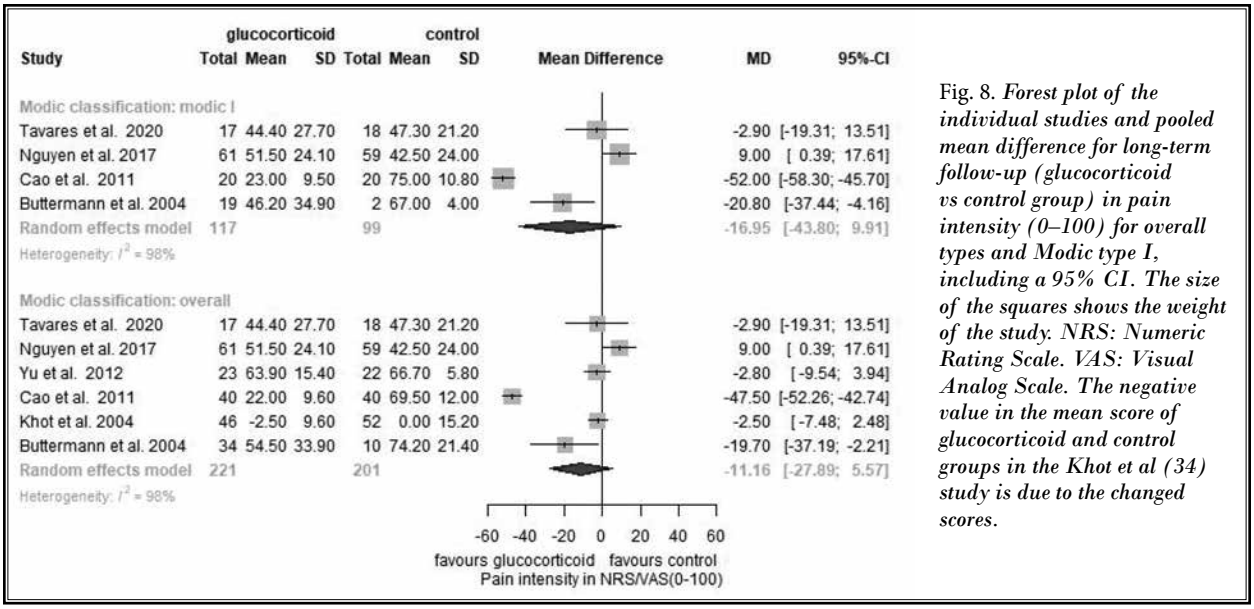

Fig. 8. *Forest plot of the individual studies and pooled mean difference for long-term follow-up (glucocorticoid vs control group) in pain intensity (0–100) for overall types and Modic type I, including a 95% CI. The size of the squares shows the weight of the study. NRS: Numeric Rating Scale. VAS: Visual Analog Scale. The negative value in the mean score of glucocorticoid and control groups in the Khot et al (34) study is due to the changed scores.*

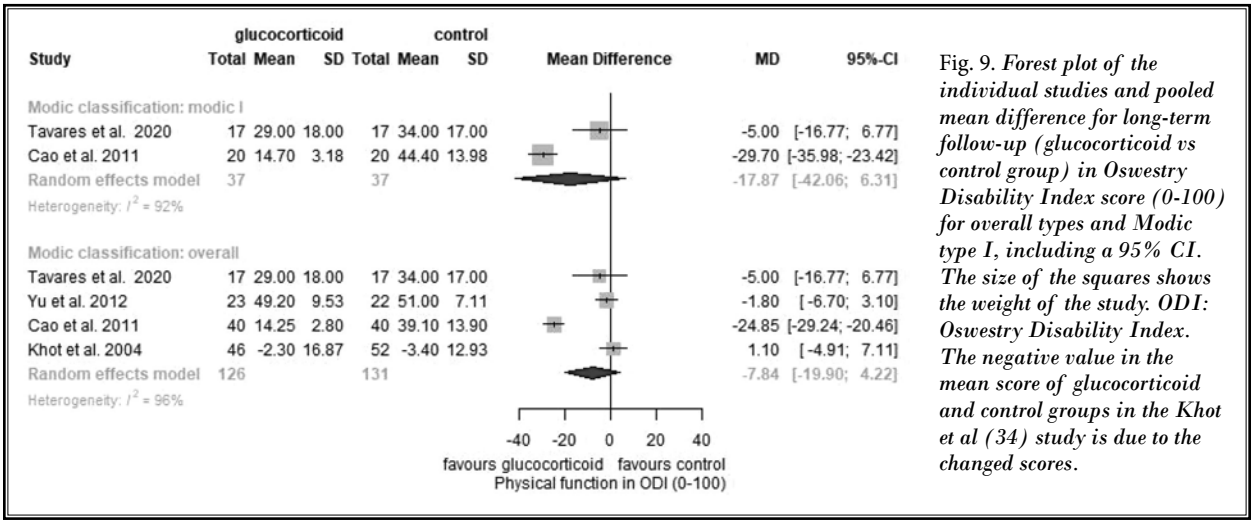

Fig. 9. *Forest plot of the individual studies and pooled mean difference for long-term follow-up (glucocorticoid vs control group) in Oswestry Disability Index score (0-100) for overall types and Modic type I, including a 95% CI. The size of the squares shows the weight of the study. ODI: Oswestry Disability Index. The negative value in the mean score of glucocorticoid and control groups in the Khot et al (34) study is due to the changed scores.*

Discussion

This systematic review and meta-analysis identified 7 RCTs on the efficacy of intradiscal glucocorticoid injection for discogenic LBP and demonstrated a strong short-term effect of IGI. The pooled data of both pain intensity scores and physical function demonstrated clinically meaningful and statistically significant effects at the short-term follow-up (< 3 months) for the IGI group in comparison to the control group (23,24,32-36). The improvement at intermediate-term follow-up (3 - < 6 months) was significant in comparison to the control group for the physical function scores, but not for pain intensity scores. However, at long-term follow-up (≥ 6 months), outcomes were not statistically significantly different in pain intensity scores and physical function, although still slightly in favor of the IGI group. Short-term pain improvement was only reported in 3 studies; the IGI groups showed a higher mean pain decrease than the control groups, however, the results were not statistically significant (23,32,35).

Recently, a systematic review and meta-analysis was published by Daste et al (37) of RCTs of intervertebral disc therapies versus placebo, active intradiscal comparator, nonintradiscal spinal injection therapies (e.g., epidural injection), or other usual care in patients with nonspecific chronic LBP (37). They defined intervertebral disc therapies as an injection of a drug,

biological product, gas, or device into the intervertebral disc. Despite a similar timeframe and study selection of RCTs, the study by Daste et al (37) not only focused on a broader range of treatments, but also on a broader range of comparators. In comparison to our study, Daste et al (37) retrieved fewer articles for the qualitative and quantitative analyses (n = 5 vs n = 7) of IGI versus control treatment, which might affect the robustness of data. They concluded that IGIs were associated with a reduction in LBP intensity at short-term follow-up in patients with nonspecific chronic LBP, but these positive effects were not sustained at the intermediate- and long-term.

In comparison to our study, Daste et al (37) did not find an improvement in physical function (called "LBP-specific activity limitations") at intermediate-term follow up. This can be explained by the fact that they did not include the study by Buttermann et al (32) in their meta-analysis. Furthermore, Daste et al (37) took the group injected with betamethasone and the group injected with betamethasone and cervus and cucumis polypeptide of the study by Cao et al (33) as the experimental group, while we used only the group injected with betamethasone (33). The decision of choosing an experimental group was based on our research question and the fact that cervus and cucumis polypeptide has an analgesic effect. Furthermore, different from our study, Daste et al (37) did not perform a subgroup analysis according to Modic changes.

It is important to underscore the relevance of IGI being superior to controls with regard to physical function in the short- and intermediate-term follow-up. Although pain intensity is a primary outcome generally used to quantify the severity of chronic LBP and the effect of its treatment, additional factors like physical function should be considered in LBP management (38). LBP is the leading cause of years lived with disability worldwide during the past 3 decades (39). Additionally, physical function is one of the predominant measures used by health insurance payers to justify approval of procedural, rehabilitation, and pharmacological therapies (40). Pain intensity and physical function are modestly associated, but over time, relate with each other in only a relatively indistinct, weak pathway (40,41). Therefore, including the outcome of physical function in chronic pain systematic reviews and meta-analyses is essential.

The place of IGI for LBP remains to be defined, given the lack of long-term benefit. The majority of treatment alternatives for discogenic LBP, like conservative care and fusion surgery, is supported by limited evidence. Previous studies have shown moderate evidence for long-term improvement with fluoroscopically guided lumbar interlaminar epidural injections (with or without steroids) in the treatment of discogenic LBP. This treatment is moderately to strongly recommended in the American Society of Interventional Pain Physicians Comprehensive Evidence-based Guidelines (42). Epidurally injected solutions probably affect the posterior longitudinal ligament and posterior annulus fibrosus (32).

Although our study suggests that IGI is a safe treatment, intradiscal injections are considered more invasive in comparison to other regularly performed spinal injections like interlaminar epidural and facet joint injections (42), and should therefore only be offered to a patient after careful consideration of the benefits and risks. While interlami-nar epidural injections and intradiscal injections share some complications, including subdural and epidural abscess and vascular and neurological injury, the risk to develop an infectious discitis is higher for intradiscal injections in comparison to epidural injections, and is intrinsic to the introduction of the needle into the intervertebral disc (42). Nevertheless, despite the fact that none of the included studies reported the use of antibiotic prophylaxis before IGI, no cases of spondylodiscitis were reported in the studies.

Additionally, the procedure of diagnostic provocative discography, a fluoroscopically guided procedure in which contrast dye is injected into the intervertebral disc to confirm the diagnosis of discogenic pain, has been associated with the acceleration of disc degeneration (43-45). As the procedure of an IGI is similar to the procedure of provocative discography (insertion of the needle in the intervertebral disc, and injection of a solution into the intervertebral disc), the risk of acceleration of disc degeneration might be likewise applicable for IGI. However, a 7-year matched cohort study demonstrated that low-pressure provocative discography, if performed according to the Spine Intervention Society/International Association for the Study of Pain standards (i.e., ≤ 3 mL intradiscal volume injection, intradiscal pressure of ≤ 50 psi above opening pressure), does not cause acceleration of disc degeneration (46). To prevent high-pressure injection, an IGI should ideally be performed with intradiscal pressure monitoring. Unfortunately, manometers for pressure monitoring are often unavailable (47). Consequently, in case manometry is not available, a

slow and gentle injection is at least advisable under conventional pres-sure (33).

The subgroup analysis of our study did not demonstrate a correlation of Modic changes and the effect of an IGI as assessed by pain intensity and physical function improvements in comparison to control treatment. Modic type I changes have been attributed to low-grade systemic and local inflammation, and even to bacterial infection, supporting a concept called "active discopathy" (11-13,48,49). The origin of this inflammation is unknown. Moreover, multiple studies have found an association between Modic changes and LBP (14-17). While the presence of a low-virulence infection might discourage using corticosteroids, no particular concerns have been raised in the literature so far, and therefore the inflammation findings provide a solid rationale for treatments targeting local inflammation, such as IGI. However, the results of a recently published systematic review by Herlin et al (50) questions associations between Modic changes on the one hand and LBP and physical function related outcomes on the other hand.

Additionally, it is well known that MRI in general provides inadequate sensitivity and specificity to accurately diagnose discogenic pain (51,52), while moderate evidence supports the diagnostic accuracy of provocative discography (53-55). A subgroup analysis did not result in a correlation of Modic changes and the efficacy of IGI. Therefore, Modic type I changes should not be a rigid requirement to determine the indication for IGI. Since the overall results didn't show any meaningful difference to those restricted to patients with Modic type I, patients without Modic type I changes may benefit from an IGI as well. The results of our systematic review and meta-analysis therefore suggest also offering an IGI to patients with LBP and DDD without Modic type I changes, but more data are needed to allow for analyses stratified on Modic types other than Modic type I.

In patients with LBP unresponsive to conservative treatment; with a medical history, clinical examination and MRI suggestive of discogenic LBP, the algorithmic approach should include diagnostic and therapeutic interventions with facet joint blocks, sacroiliac joint injections, and lumbar interlaminar epidural injections (42). If these interventions are negative or ineffective, provocative discography could be offered as the next step in the diagnostic algorithm to confirm the diagnosis of discogenic LBP. A positive discography can be immediately followed by an IGI, without adding substantial risks, time, or significant expense (35). Given the short- to intermediate-term improvement after IGI demonstrated by our study, repetition of a responsive IGI can be considered in cases of recurring of LBP, leading possibly to a reduction in major low-back surgery procedures.

The emerging area of vertebrogenic pain likely to some extent overlaps with discogenic pain. Radiofrequency ablation of the basivertebral pain led to significant improvement in pain and function in patients with chronic vertebrogenic-related LBP in 2 controlled studies and a trial against best medical therapy (56-58).

Limitations

Some limitations and biases of our systematic review and meta-analysis should be considered. A limited number of studies were available for the systematic review and the meta-analysis for evaluating IGI versus control for LBP; consequently, we could not evaluate the publication bias using a funnel plot. Moreover, in some of the meta-analyses, substantial statistical heterogeneity was detected among the included studies ($I^2 > 50\%$). The heterogeneity can be explained in part by the variety of glucocorticoids and controls used among the studies, including types and doses and population diversity. However, the number of studies that we included was insufficient to explore between-study heterogeneity in greater detail.

Conclusion

Despite limited data, we conclude that IGI is superior to control treatment for discogenic LBP intensity scores at short-term follow-up. Furthermore, the treatment continues to be superior with regard to physical function at intermediate-term follow-up. However, after 6 months of follow-up, the patients treated with IGI showed similar results to the control groups. Modic type classification seems to have a limited clinical relevance with regard to the effect of an IGI since all patient groups with LBP and DDD included in these studies seem to benefit from an IGI. We suggest further studies with standardized settings to shed more light on this topic.

References

1. Cheung KMC, Karppinen J, Chan D, et al. Prevalence and pattern of lumbar magnetic resonance imaging changes in a population study of one thousand forty-three individuals. *Spine (Phila Pa 1976)* 2009; 34:934-940.
2. DePalma MJ, Ketchum JM, Saullo T. What is the source of chronic low back pain and does age play a role? *Pain Med* 2011; 12:224-233.
3. Schwarzer AC, Aprill CN, Derby R, Fortin J, Kine G, Bogduk N. The relative contributions of the disc and zygapophyseal joint in chronic low back pain. *Spine (Phila Pa 1976)* 1994; 19:801-806.
4. Verrills P, Nowesenitz G, Barnard A. Prevalence and characteristics of discogenic pain in tertiary practice: 223 consecutive cases utilizing lumbar discography. *Pain Med* 2015; 16:1490-1499.
5. Fujii K, Yamazaki M, Kang JD, et al. Discogenic back pain: Literature review of definition, diagnosis, and treatment. *JBMR Plus* 2019; 3:e10180.
6. Kallewaard JW, Terheggen MAMB, Groen GJ, et al. Discogenic low back pain. *Pain Pract* 2010; 10:560-579.
7. Peng BG. Pathophysiology, diagnosis, and treatment of discogenic low back pain. *World J Orthop* 2013; 4:42-52.
8. Zhao L, Manchikanti L, Kaye AD, Abd-Elsayed A. Treatment of discogenic low back pain: Current treatment strategies and future options—A literature review. *Curr Pain Headache Rep* 2019; 23:86.
9. Modic MT, Steinberg PM, Ross JS, Masaryk TJ, Carter JR. Degenerative disk disease: Assessment of changes in vertebral body marrow with MR imaging. *Radiology* 1988;166:193-199.
10. Yu LP, Qian WW, Yin GY, Ren YX, Hu ZY. MRI Assessment of lumbar intervertebral disc degeneration with lumbar degenerative disease using the Pfirrmann grading systems. *PLoS ONE* 2012; 7:e48074.
11. Bailly F, Maigne JY, Genevay S, et al. Inflammatory pain pattern and pain with lumbar extension associated with Modic 1 changes on MRI: A prospective case–control study of 120 patients. *Eur Spine J* 2014; 23:493-497.
12. Rannou F, Ouanes W, Boutron I, et al. High-sensitivity C-reactive protein in chronic low back pain with vertebral end-plate Modic signal changes. *Arthritis Rheum* 2007; 57:1311-1315.
13. Ohtori S, Inoue G, Ito T, et al. Tumor necrosis factor-immunoreactive cells and PGP 9.5-immunoreactive nerve fibers in vertebral endplates of patients with discogenic low back pain and Modic Type 1 or Type 2 changes on MRI. *Spine (Phila Pa 1976)* 2006; 31:1026-1031.
14. Brinjikji W, Diehn FE, Jarvik JG, et al. MRI findings of disc degeneration are more prevalent in adults with low back pain than in asymptomatic controls: A systematic review and meta-analysis. *AJNR Am J Neuroradiol* 2015; 36:2394-2399.
15. Jensen RK, Leboeuf-Yde C, Wedderkopp N, Sorensen JS, Jensen TS, Manniche C. Is the development of Modic changes associated with clinical symptoms? A 14-month cohort study with MRI. *Eur Spine J* 2012; 21:2271-2279.
16. Kääpä E, Luoma K, Pitkäniemi J, Kerttula L, Grönblad M. Correlation of size and type of Modic types 1 and 2 lesions with clinical symptoms: A descriptive study in a subgroup of patients with chronic low back pain on the basis of a university hospital patient sample. *Spine (Phila Pa 1976)* 2012; 37:134-139.
17. Luoma K, Vehmas T, Kerttula L, Grönblad M, Rinne E. Chronic low back pain in relation to Modic changes, bony endplate lesions, and disc degeneration in a prospective MRI study. *Eur Spine J* 2016; 25:2873-2881
18. van Middelkoop M, Rubinstein SM, Kuijpers T, et al. A systematic review on the effectiveness of physical and rehabilitation interventions for chronic non-specific low back pain. *Eur Spine J* 2011; 20:19-39.
19. Guo X, Ding W, Liu L, Yang S. Intradiscal methylene blue injection for discogenic low back pain: A meta-analysis. *Pain Pract* 2019; 19:118-129.
20. Schneider BJ, Hunt C, Conger A, et al. The effectiveness of intradiscal biologic treatments for discogenic low back pain: A systematic review. *Spine J* 2022; 22:226-237.
21. Sconza C, Leonardi G, Kon E, et al. Oxygen-ozone therapy for the treatment of low back pain: A systematic review of randomized controlled trials. *Eur Rev Med Pharmacol Sci* 2021; 25:6034-6046.
22. Gilligan CJ, Cohen SP, Fischetti VA, Hirsch JA, Czaplewski LG. Chronic low back pain, bacterial infection and treatment with antibiotics. *Spine J* 2021; 21:903-914.
23. Nguyen C, Boutron I, Baron G, et al. Intradiscal glucocorticoid injection for patients with chronic low back pain associated with active discopathy: A randomized trial. *Ann Intern Med* 2017; 166: 547-556.
24. Tavares I, Thomas E, Cyteval C, et al. Intradiscal glucocorticoids injection in chronic low back pain with active discopathy: A randomized controlled study. *Ann Phys Rehabil Med* 2021; 64:101396.
25. McInnes MDF, Moher D, Thombs BD, et al. Preferred Reporting Items for a Systematic Review and Meta-analysis of Diagnostic Test Accuracy Studies: The PRISMA-DTA Statement. *JAMA* 2018; 319:388-396.
26. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *Int J Surg* 2010; 8:336-341.
27. Center for Evidence-based Medicine. What if there's only a graph? *University of Oxford* 2019. www.cebm.ox.ac.uk/resources/data-extraction-tips-meta-analysis/only-a-graph.
28. Sterne JAC, Savović J, Page MJ, et al. RoB 2: A revised tool for assessing risk of bias in randomised trials. *BMJ* 2019; 366:l4898.
29. Ostelo RWJG, de Vet HCW. Clinically important outcomes in low back pain. *Best Pract Res Clin Rheumatol* 2005; 19:593-607.
30. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002; 21:1539-1558.
31. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol* 2014; 14:135.
32. Buttermann GR. The effect of spinal steroid injections for degenerative disc disease. *Spine J* 2004; 4:495-505.
33. Cao P, Jiang L, Zhuang C, et al. Intradiscal injection therapy for degenerative chronic discogenic low back pain with end plate Modic changes. *Spine J* 2011; 11:100-106.
34. Khot A, Bowditch M, Powell J, Sharp D. The use of intradiscal steroid therapy for lumbar spinal discogenic pain: A randomized controlled trial. *Spine (Phila Pa 1976)* 2004; 29:833-836.
35. Simmons JW, McMillin JN, Emery SF,

Kimmich SJ. Intradiscal steroids. A prospective double-blind clinical trial. *Spine (Phila Pa 1976)* 1992; 17:S172-S175.

36. Yu Y, Liu W, Song D, Guo Q, Jia L. Diagnosis of discogenic low back pain in patients with probable symptoms but negative discography. *Arch Orthop Trauma Surg* 2012; 132:627-632.
37. Daste C, Laclau S, Boisson M, et al. Intervertebral disc therapies for non-specific chronic low back pain: A systematic review and meta-analysis. *Ther Adv Musculoskelet Dis* 2021; 13:1759720X2110280.
38. Tagliaferri SD, Miller CT, Owen PJ, et al. Domains of chronic low back pain and assessing treatment effectiveness: A clinical perspective. *Pain Pract* 2020; 20:211-225.
39. James SL, Abate D, Abate KH, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: A systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2018; 392:1789-1858.
40. Karayannis NV, Sturgeon JA, Chih-Kao M, Cooley C, Mackey SC. Pain interference and physical function demonstrate poor longitudinal association in people living with pain: A PROMIS investigation. *Pain* 2017; 158:1063-1068.
41. Dworkin RH, Turk DC, Farrar JT, et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain* 2005; 113:9-19.
42. Manchikanti L, Knezevic NN, Navani A, et al. Epidural interventions in the management of chronic spinal pain: American Society of Interventional Pain Physicians (ASIPP) Comprehensive Evidence-based Guidelines. *Pain Physician* 2021; 24:S27-S208.
43. Carragee EJ, Don AS, Hurwitz EL, Cuellar JM, Carrino J, Herzog R. 2009 ISSLS Prize winner: Does discography cause accelerated progression of degeneration changes in the lumbar disc: A ten-year matched cohort study. *Spine (Phila Pa 1976)* 2009; 34:2338-2345.
44. Cuellar JM, Stauff MP, Herzog RJ, Carrino JA, Baker GA, Carragee EJ. Does provocative discography cause clinically important injury to the lumbar intervertebral disc? A 10-year matched cohort study. *Spine J* 2016; 16:273-280.
45. Koetsier E, Kallewaard JW, Maino P. Commentary on: Does provocative discography cause clinically important injury to the lumbar intervertebral disc? A 10-year matched cohort study, by Cueller et al. *Spine J* 2016. *Spine J* 2017; 17:610-611.
46. McCormick ZL, Lehman VT, Plastaras CT, et al. Low-pressure lumbar provocation discography according to Spine Intervention Society/International Association for the Study of Pain standards does not cause acceleration of disc degeneration in patients with symptomatic low back pain: A 7-year matched cohort study. *Spine (Phila Pa 1976)* 2019; 44:E1161-E1168.
47. Stretanski MF, Vu L. Fluoroscopy discography assessment, protocols, and interpretation. In: *StatPearls* [Internet]. Treasure Island, FL: StatPearls Publishing; 2022. www.ncbi.nlm.nih.gov/books/NBK572119/
48. Albert HB, Lambert P, Rollason J, et al. Does nuclear tissue infected with bacteria following disc herniations lead to Modic changes in the adjacent vertebrae? *Eur Sine J* 2013; 22:690-696.
49. Nguyen C, Poiraudeau S, Rannou F. From Modic 1 vertebral-endplate subchondral bone signal changes detected by MRI to the concept of 'active discopathy.' *Ann Rheum Dis* 2015; 74:1488-1494.
50. Herlin C, Kjaer P, Espeland A, et al. Modic changes—Their associations with low back pain and activity limitation: A systematic literature review and meta-analysis. *PloS One* 2018 ;13:e0200677.
51. Brinjikji W, Luetmer PH, Comstock B, et al. Systematic literature review of imaging features of spinal degeneration in asymptomatic populations. *AJNR Am J Neuroradiol* 2015; 36:811-816.
52. Schwarzer AC, Aprill CN, Derby R, Fortin J, Kine G, Bogduk N. The prevalence and clinical features of internal disc disruption in patients with chronic low back pain: *Spine (Phila Pa 1976)* 1995; 20:1878-1883.
53. Manchikanti L, Benyamin RM, Singh V, et al. An update of the systematic appraisal of the accuracy and utility of lumbar discography in chronic low back pain. *Pain Physician* 2013; 16:SE55-SE95.
54. Manchikanti L, Soin A, Benyamin RM, et al. An update of the systematic appraisal of the accuracy and utility of discography in chronic spinal pain. *Pain Physician* 2018; 21:91-110.
55. Wolfer LR, Derby R, Lee JE, Lee SH. Systematic review of lumbar provocation discography in asymptomatic subjects with a meta-analysis of false-positive rates. *Pain Physician* 2008; 11:513-538.
56. Fischgrund JS, Rhyne A, Franke J, et al. Intraosseous basivertebral nerve ablation for the treatment of chronic low back pain: A prospective randomized double-blind sham-controlled multi-center study. *Eur Spine J* 2018; 27:1146-1156.
57. Khalil JG, Smuck M, Koreckij T, et al. A prospective, randomized, multicenter study of intraosseous basivertebral nerve ablation for the treatment of chronic low back pain. *Spine J* 2019; 19:1620-1632.
58. Koreckij T, Kreiner S, Khalil JG, Smuck M, Markman J, Garfin S. Prospective, randomized, multicenter study of intraosseous basivertebral nerve ablation for the treatment of chronic low back pain: 24-Month treatment arm results. *N Am Spine Soc J* 2021; 8:100089.

Appendix A. ***PubMed and Embase search strategy.***

No.	Query
PubMed	
#1	('low back pain ′ OR 'back pain' OR 'intervertebral disc degeneration' OR 'discogenic pain')
#2	('injections' OR 'infiltration')
#3	('intradiscal' OR 'intra-discal')
#4	('randomized controlled trial' OR 'controlled clinical trial')
#5	#1 and #2 and #3 and #4
Embase	
#1	('low back pain' OR 'backache' OR 'intervertebral disk degeneration' OR 'discogenic pain')
#2	('injection' OR 'infiltration')
#3	('intradiscal drug administration')
#4	('randomized controlled trial' or 'controlled clinical trial')
#5	#1 and #2 and #3 and #4