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Longitudinal Relationship Between Reduced Modic Change Edema and Disability and Pain in Patients With Chronic Low Back Pain

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Study Design. Secondary analyses of a randomized trial [Antibiotics In Modic changes (MCs) study].

Objective. To assess whether or not reduced MC edema over time is related to reduced disability and pain in patients with chronic low back pain (LBP).

Summary of Background Data. It is not clear whether or not reduced MC edema implies improved clinical outcomes.

Patients and Methods. Linear regression was conducted separately in 2 subgroups with MC edema at baseline on short tau inversion recovery (STIR) or T1/T2-weighted magnetic resonance imaging, respectively. Independent variable: reduced edema (yes/no) at 1 year on STIR or T1/T2-series, respectively. Dependent variable: 1-year score on the Roland-Morris Disability Questionnaire (RMDQ), Oswestry Disability Index (ODI), or 0 to 10 numeric rating scale for LBP intensity, adjusted for the baseline score, age, smoking, body mass index, physical workload, and baseline edema on STIR (STIR analysis only). Post hoc, we, in addition, adjusted all analyses for baseline edema on STIR, treatment group (amoxicillin/placebo), and prior disc surgery—or for disc degeneration.

Results. Among patients with MC edema on STIR at baseline (n = 162), reduced edema on STIR was not significantly related to the RMDQ (*B*: −1.0, 95% CI: −2.8, 0.8; $P = 0.27$), ODI (*B*:−1.4, 95% CI: −5.4, 2.6; $P = 0.50$), or LBP intensity scores (*B*: −0.05, 95% CI: −0.8, 0.7; $P = 0.90$) after 1 year. Among patients with MC edema on T1/T2-series at baseline (n = 116), reduced edema on T1/T2 (*i.e.*, reduced volume of the type 1 part of MCs) was not significantly related to RMDQ (*B:* −1.7, 95% CI: −3.8, 0.3; $P = 0.10$) or ODI score (*B*: −2.3, 95% CI: −7.1, 2.5; $P = 0.34$) but was significantly related to LBP intensity at 1 year (*B*: −0.9, 95% CI: −1.8, −0.04; $P = 0.04$; correlation coefficient: 0.24). The post hoc analyses supported these results.

Conclusion. Reduced MC edema over 1 year was not significantly associated with pain-related disability but was (on T1/T2-series) significantly but weakly related to reduced LBP intensity.

Key words: amoxicillin, disability, edema, low back pain, magnetic resonance imaging, Modic changes, prospective studies, randomized controlled trial, spine, STIR

Level of Evidence. 3.

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The device(s)/drug(s) that is/are the subject of this manuscript is/are exempt from FDA or corresponding national regulations because The Norwegian Medicines Agency (SLV; reference No 14/01368-11; EudraCT No 2013-004505-14) approved the use of amoxicillin in this trial before it started.

The authors report no conflicts of interest.

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Modic changes (MCs) are vertebral bone marrow changes extending from the endplate, classified on T1 and T2-weighted magnetic resonance imaging

(MRI) as type 1 (edema type, MC1), type 2 (fatty type, MC2), and type 3 (sclerotic type).[1,2] Some data suggest that MC1 may be associated with the intensity of low back pain (LBP)[3–6] and pain-related disability.[4,7,8] However, most studies of the associations between MCs and LBP or disability were cross-sectional, and their results diverged.[9–14] Few studies have assessed the course of MC edema over time in relation to patient-reported outcomes in LBP, and again with conflicting results.[4,8,15,16] These studies adjusted for none or a few potential confounders and used the T1/T2 series without fat suppression. It is also relevant to apply short tau inversion recovery (STIR) or other fat-suppressed MRI sequences that are more sensitive to edema in MCs.[17]

The present study used data from the Antibiotics In Modic (AIM) changes study, which included T1/T2-series and STIR at baseline and 1-year follow-up. The AIM study tested the effect of 100 days of treatment with amoxicillin *versus* placebo in patients with chronic LBP and MC1 or MC2 at the level of a previous lumbar disc herniation. The hypothesis was that MCs may be due to low-grade bacterial disc infection[18] caused by hematogenous contamination facilitated by neovascularization associated with disc herniation.[19] At 1 year, the MC1 group had a small, clinically insignificant effect of amoxicillin on patient-reported disability.[20] Subsequent analysis also indicated an effect in a small subgroup with abundant baseline MC edema on STIR ("STIR3" group, defined further).[21] However, amoxicillin did not reduce MC edema compared with placebo.[22] The purpose of the current study was to assess whether or not reduced MC edema over time is related to reduced disability and pain in patients with chronic LBP.

PATIENTS AND METHODS

The AIM Study

Patients were included in the AIM study from hospital outpatient clinics in Norway from June 2015 to September 2017.[18,20] The inclusion criteria were age 18 to 65 years, LBP for more than 6 months with an intensity of at least 5 (mean score on three 0–10 numerical rating scales), lumbar disc herniation on MRI in the preceding 2 years, and MC1 or MC2 (with height $\geq 10\%$ of the vertebral body height and diameter > 5 mm) at the previously herniated disc level. A complete list of eligibility criteria (Supplemental Table A1 in Supplemental File, Supplemental Digital Content 1, http://links.lww.com/BRS/C224) and trial methods have been published.[20]

Briefly, patients in the AIM study (n = 180) were randomized to receive oral amoxicillin 750 mg or placebo (maize starch) three times daily for 100 days. Allocation was concealed, centrally administered, and stratified according to prior disc surgery (yes/no) and MC type (any MC1, n = 118 or MC2 only, n = 62) at the previously herniated disc level. All care providers, research staff, statisticians, and patients were blinded to treatment allocation during data collection. Treatments other than the study medication (amoxicillin or placebo) were registered monthly during 1-year follow-up.

The primary endpoint was pain-related disability at 1 year, scored on the Norwegian version of the Roland-Morris Disability Questionnaire (RMDQ; 0–24 scale).[23,24] Secondary outcomes included the Oswestry Disability Index (ODI) 2.0 (0–100 scale)[23,25] and LBP intensity (mean 0–10 numerical rating scale score for current LBP, worst LBP within the last 2 wk, and usual/mean LBP within the last 2 wk). Higher scores indicate a worse disability or LBP intensity.

Lumbar spine MRI was performed at baseline and 1-year follow-up using identical MRI protocols[26] and the same type of 1.5-T scanner (Magnetom Avanto B19; Siemens Healthineers, Erlangen, Germany; Avanto fit E11 for 16 follow-up examinations). All examinations included sagittal T1 and T2-weighted fast spin-echo ("T1/T2") and sagittal STIR images, obtained using the integrated spine array coil. Surface coils were not used. The echo time (ms)/repetition time (ms) was 11/575 for T1, 87/3700 for T2, and 70/5530 for STIR. Echo train lengths were 5, 17, and 20 for T1, T2, and STIR, respectively. T1/T2 had matrix 384×269. STIR had a 320×224 matrix and an inversion time of 160 ms. All sequences had a slice thickness of 4 mm, interslice gap of 0.4 mm, and field of view of 300×300 mm.

The AIM trial, the current study, and statistical analysis plans (SAPs) are registered at ClinicalTrials.gov (identifier: NCT02323412). Written informed consent was obtained from all the patients before inclusion.

The Current Study

This study focused on MRI findings at the index level(s), that is, level(s) with a prior disc herniation and MC1 or MC2 at baseline. All MC-related MRI variables were defined in the SAP (available at ClinicalTrials.gov) and have been described,[22,26] and are shown in Table 1. Three radiologists blinded to clinical outcome and treatment group independently rated all MRIs using clinical picture archiving and communication system workstations. Each radiologist had more than 10 years of experience in spinal MRI.

Changes on MRI were visually rated by comparing the 1-year and baseline images side-by-side. Changes in the volume or intensity of MC edema on STIR (STIR change) and in the volume of MC edema on T1/T2 (*i.e.*, change in the volume of the type 1 part of MCs, MC1 change) were classified as reduced, unchanged, or increased. Examples of reduced MC edema on STIR and T1/T2 are shown in Figure 1.

The 3 radiologists' majority or median rating was used in the analyses. We also used reported data for a composite categorical variable (STIR 1/2/3)[21] to adjust for baseline MC edema on STIR ("STIR3," yes or no) in relevant analyses. STIR3 represented the most abundant edema and is defined in Table 1. The interrater agreement (mean kappa) among the 3 radiologists was very good for the

TABLE 1. MRI Variables

	Description	Categories
MCs	T1/T2 signal changes in the vertebral bone marrow that extend from the endplate, but are not separated from the endplate, abutting the endplate with a smaller base than height, or extending through the endplate	Yes or no
MC1 = MC edema on T1/T2	MC with low T1 signal and high T2 signal compared with normal vertebral body marrow	Yes or no
MC2	MC with high T1 signal and high or isointense T2 signal, and borderline type 1 *vs*. type 2 MCs with high T2 signal but near isointense T1 signal	Yes or no
MC edema on STIR	MC-related high STIR signal compared with normal vertebral body marrow	Yes or no
Abundant baseline MC edema on STIR ("STIR3")	STIR3 (most abundant edema) implies that the high STIR signal (MC edema on STIR) fulfills all the following criteria: volume $\geq$25% and height $>$50% of the vertebral body, maximum intensity increase $\geq$25% (0%, normal vertebral body marrow; 100%, cerebrospinal fluid), and presence on both sides of the disc	Yes or no
Change in MC edema at each endplate	A change (*e.g.*, reduction) in MC edema is noted if seen on $\geq$2 slices and on $\geq$2 more slices than any opposite change (*e.g.*, increase)	Reduced, unchanged, or increased
Change in MC edema in each patient	Noted as "unchanged" if unchanged at all endplates, "reduced" if reduced at $\geq$1 endplate and increased at 0 endplates, and "increased" if increased at $\geq$1 endplate and reduced at 0 endplates. In a patient with both reductions and increases, a change is noted if seen on $\geq$2 more slices than the opposite change	Reduced, unchanged, or increased; dichotomized as reduced or not in regression analyses
STIR change	Change in volume or intensity of MC edema on STIR from baseline to 1 yr follow-up per patient	Reduced, unchanged, or increased
MC1 change	Change in volume of MC edema on T1/T2, that is, changes in the volume of the type 1 part of MCs, from baseline to 1 yr follow-up per patient	Reduced, unchanged, or increased
DD grade	Rated on midsagittal T2 images as Pfirrmann grade 1 (normal), 2, 3, 4, or 5 (worst: collapsed disc, interpreted as $\geq$50% reduced disc height; lost distinction between nucleus pulpous and annulus fibrosus)	Grade 1, 2, 3, 4, or 5

DD indicates disc degeneration; MC, Modic change; MC1, MC type 1; MC2, MC type 2; MRI, magnetic resonance imaging; STIR, short tau inversion recovery; T1/T2, T1/T2-weighted.

presence of MC edema on STIR/MC1 (0.86/0.81)[21] and good for STIR change/MC1 change (0.71/0.74).[22]

Two of the radiologists rated the highest disc degeneration (DD) Pfirrmann grade (Table 1) at an index level with good interrater agreement (linearly weighted kappa 0.66 in the current study sample, n = 162). Disagreements were solved in consensus and relevant analyses were adjusted for DD grade.

Predefined Hypotheses

Our research hypotheses, predefined in the SAP, were as follows.

- (A) Reduced MC edema on STIR from baseline to 1-year follow-up is related to lower RMDQ score at 1-year follow-up adjusted for the baseline score (hypothesis also included in the AIM study protocol[18]).
- (B) Reduced MC edema on T1/T2 from baseline to 1-year follow-up is related to lower RMDQ score at 1-year follow-up adjusted for the baseline score (hypothesis not included in the AIM study protocol).

The corresponding statistical null hypothesis was that reduced MC edema is not related to the RMDQ score. The statistical 2-sided alternative hypotheses state that such a relationship exists (in any direction).

Analyses

We analyzed 2 overlapping subgroups according to the presence of MC edema at baseline on STIR (STIR subgroup) or T1/T2, that is, MC1 (MC1 subgroup). Patients who during the 1-year follow-up received a specific back pain diagnosis (n = 1) or back surgery (n = 1) were not analyzed (Figure 2).

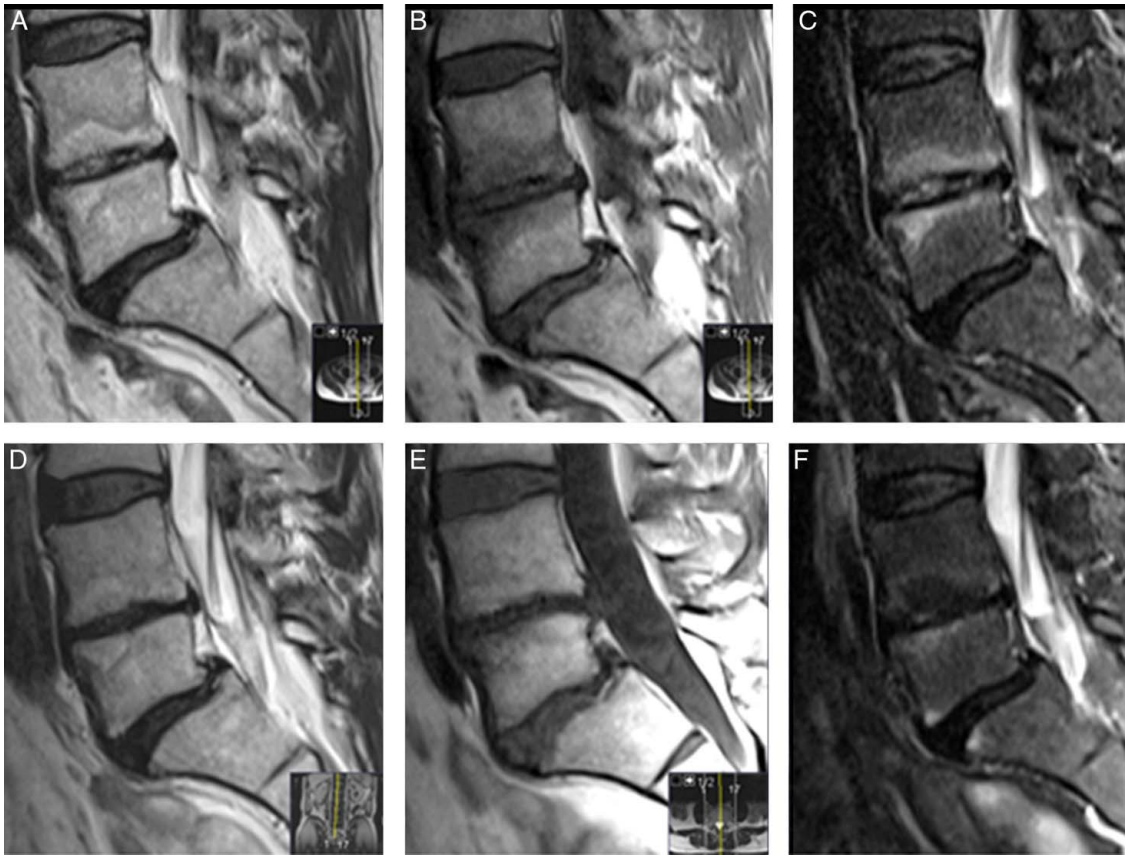

Figure 1. Examples of reduced MC edema. A–F, Example of MC edema at L4/L5. Baseline MRI showing MC edema with high T2 signal (A), low T1 signal (B) (*i.e.*, MC1), and high signal on STIR (C). One-year MRI shows unchanged T2 signal (D) and higher signal with a hyperintense area on T1 (E) (*i.e.* reduced area of the type 1 part of the MC) and reduced area and intensity of the high signal on STIR (*i.e.* reduced MC edema on STIR) (F). MC indicates Modic change; MC1, MC type 1; MRI, magnetic resonance imaging; STIR, short tau inversion recovery; T1/T2, T1-weighted/ T2-weighted. full color online

To assess hypotheses (A) and (B), linear regression was performed in the STIR and MC1 subgroups, respectively, using the 1-year RMDQ score as the dependent variable adjusted for the RMDQ baseline score. Independent variables were STIR change or MC1 change, which were dichotomized into reduced or not reduced (*i.e.*, unchanged or increased). Linear regression was also performed using the 1-year ODI or LBP intensity score as the dependent variable. The regression models were adjusted for age, smoking, body mass index, heavy physical work/lifting, and (in the STIR subgroup only) abundant baseline edema on STIR (STIR3, yes/no). Post hoc, we, in addition, adjusted all models for abundant baseline edema on STIR, treatment group (amoxicillin/placebo), and prior disc surgery—or for highest index level DD grade. Potential interactions between reduced edema and baseline edema or treatment group were also examined. All predefined and post hoc regression analyses are detailed in Table 2.

We report the unstandardized regression coefficient *B* with a 95% CI and *P* value, as stated in the SAP. Post hoc, point-biserial correlations between reduced MC edema (yes/no) and the reduction in RMDQ, ODI, and LBP intensity scores after 1 year were assessed using Pearson *r*.

We used a Bonferroni corrected significance level of 0.05/7 = 0.007 for hypothesis (A), as it was ranked as the seventh hypothesis in the AIM study protocol.[18] The significance level was otherwise kept at 0.05 (2-sided), as stated in the SAP, reducing the risk of overlooking potentially relevant associations while increasing the chance of observing spurious associations. Statistical tests were performed after multiple imputations of missing values (Supplemental Table A2 in Supplemental File, Supplemental Digital Content 2, http://links.lww.com/BRS/C225). SPSS 26 (IBM Corp, NY) was used for analyses and imputations.

The analyzed subgroups had fixed sample sizes, and no power calculations were conducted.

RESULTS

Baseline characteristics of the STIR subgroup (n = 162) and MC1 subgroup (n = 116) are shown in Supplemental Table A3 in Supplemental File (Supplemental Digital Content 3, http://links.lww.com/BRS/C226). The STIR subgroup included all the patients in the MC1 subgroup. One-year MRI was performed in 95% (154/162) of patients in the STIR subgroup and 94% (109/116) of patients in the MC1 subgroup.

The changes in the RMDQ, ODI, and LBP intensity scores according to changes in MC edema are shown in Table 3 and Table 4. Score reductions generally differed little between the groups with reduced, unchanged, or

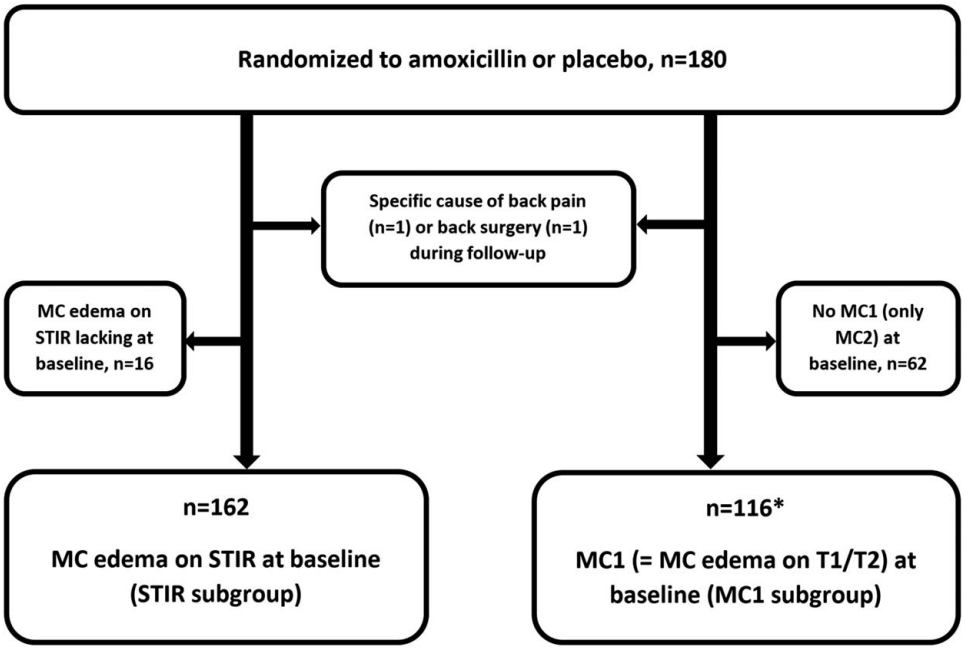

Figure 2. Definition of study subgroups. *Corrected from n = 117 in the SAP; one patient with spondylarthritis was excluded. MC indicates Modic change; MC1, MC type 1; MC2, MC type 2; SAP, statistical analysis plan; STIR, short tau inversion recovery; T1/T2, T1-weighted and T2-weighted.

increased MC edema, and they correlated weakly with reduced MC edema ($r \leq 0.23$, Table 5).

Treatments other than the study medication were similar during the 1-year follow-up for patients with and without reduced MC edema and correlated weakly with the clinical outcomes (Supplemental Table A4, Supplemental Digital Content 4, http://links.lww.com/BRS/C227, Table A5, Supplemental Digital Content 5, http://links.lww.com/BRS/C228, and Table A6 in Supplemental File, Supplemental Digital Content 6, http://links.lww.com/BRS/C229).

STIR Subgroup

Reduced MC edema on STIR was not significantly related to the RMDQ score after 1 year, neither in the predefined final regression model (*B*: −1.0, 95% CI: −2.8, 0.8; $P = 0.27$) nor in the post hoc models (Table 5). Reduced STIR edema showed no significant interaction with abundant baseline STIR edema (STIR3 or not; $P = 0.32$) or with the treatment group ($P = 0.63$; details in Supplemental Data File linear regression analyses, Supplemental Digital Content 7, http://links.lww.com/BRS/C230).

Reduced MC edema on STIR was not significantly related to ODI or LBP intensity scores (Table 5).

MC1 Subgroup

Reduced volume of the type 1 part of MCs was significantly related to the LBP intensity score after 1 year (*B*: −0.9, 95% CI: −1.8, −0.04; $P = 0.04$), but not to the RMDQ or ODI score (Table 5, predefined final regression models). These findings were retained in the post hoc regression models (Table 5). The correlation between reduced MC1 volume (yes/no) and the reduction in LBP intensity was weak ($r = 0.23$).

DISCUSSION

This study assessed whether reduced MC edema on MRI was related to reduced disability and pain over 1 year. Reduced MC edema on the STIR or T1/T2 series was not significantly related to reduced disability. Reduced volume of the type 1 part of MCs on the T1/T2 series was associated weakly with reduced LBP intensity.

We are not aware of any other studies on the relationship between reduced MC edema on STIR and patient-reported outcomes. A few studies have examined changes in MC1 over time on the T1/T2 series in relation to disability and/or pain intensity, with conflicting results.[4,8,15,16] These studies and relevant studies by Cevik and Yilmaz[27] and Tamai *et al*[28] are summarized in Supplemental File (Supplemental Table A7, Supplemental Digital Content 8, http://links.lww.com/BRS/C231). Further, we compare our results with those of the previous studies. These comparisons are complicated by differences in sample size, eligibility criteria, MRI assessment, and analyses (method, variables, and adjustments).

Our finding that the reduced type 1 part of MCs was related to reduced LBP intensity agrees with the results reported by Luoma *et al*.[4] However, Jensen *et al*[15] found no association between reduced LBP intensity (yes/no) at 14 months and a reduced height score (yes/no) of the largest MC1 on a 1 to 4 scale. Unlike our study, they dichotomized the LBP variable, only analyzed the largest MC1, and used 0.2 T MRI, which overestimates MC1 presence compared with 1.5 T MRI[29] (used in our study). Interestingly, reduced LBP intensity was less likely in patients with MC1 both at baseline and follow-up *versus* patients without MC1 at both time points.[15] Cevik and Yilmaz[27] reported similar results. In a small subsample (n = 28), Mitra *et al*[16] found a trend ($P = 0.08$) of lower pain severity scores at

TABLE 2. Linear Regression Analyses—Predefined and Post hoc

Analysis	Variables
STIR subgroup (n = 162)	
Predefined (model "a," used to assess hypothesis "A")	Dependent: RMDQ score at 1 yr or intensity of MC edema on STIR after 1 yr (STIR change, dichotomized into reduced or not reduced), baseline RMDQ score, age, smoking (yes/no), body mass index, heavy physical work/lifting (yes/no), STIR3 (yes/no)
Predefined (used to assess interaction)	Dependent: RMDQ score at 1 yr. Independent: as in model "a" plus the interaction term "STIR3×STIR change." R^2 adjusted for the number of independent variables in the model calculated to assess model improvement
Post hoc (used to assess interaction)	Dependent: RMDQ score at 1 yr. Independent: as in the model "a" plus treatment group (amoxicillin or placebo), and the interaction term "treatment group×STIR change" (but not "STIR3×STIR change")
Post hoc	Dependent: RMDQ score at 1 yr. Independent: as in model "a" plus treatment group and prior disc surgery (yes/no)
Post hoc	Dependent: RMDQ score at 1 yr. Independent: as in model "a" plus DD
Predefined	Dependent: ODI score at 1 yr. Independent: STIR change (reduced or not reduced), baseline ODI score, age, smoking, body mass index, heavy physical work/lifting, STIR3
Post hoc	Dependent: ODI score at 1 yr. Independent: as in the preceding analysis plus treatment group and prior disc surgery
Post hoc	Dependent: ODI score at 1 yr. Independent: as in the preceding analysis but including DD instead of the treatment group and prior disc surgery
Predefined	Dependent: LBP intensity score at 1 yr. Independent: STIR change (reduced or not reduced), baseline LBP intensity score, age, smoking, body mass index, heavy physical work/lifting, STIR3
Post hoc	Dependent: LBP intensity score at 1 yr. Independent: as in the preceding analysis plus treatment group and prior disc surgery
Post hoc	Dependent: LBP intensity score at 1 yr. Independent: as in the preceding analysis but including DD instead of the treatment group and prior disc surgery
MC1 subgroup (n = 116)	
Predefined (model "b," used to assess hypothesis "B")	Dependent: RMDQ score at 1 yr. Independent: change in volume of MC edema on T1/T2 series (*i.e.*, change in volume of the type 1 part of MCs, MC1 change, dichotomized into reduced or not reduced), baseline RMDQ score, age, smoking, body mass index, heavy physical work/lifting
Post hoc	Dependent: RMDQ score at 1 yr. Independent: as in model "b" plus treatment group, prior disc surgery, and STIR3
Post hoc	Dependent: RMDQ score at 1 yr. Independent: as in model "b" plus DD
Predefined	Dependent: ODI score at 1 yr. Independent: MC1 change (reduced or not reduced), baseline ODI score, age, smoking, body mass index, heavy physical work/lifting
Post hoc	Dependent: ODI score at 1 yr. Independent: as in the preceding analysis plus treatment group, prior disc surgery, and STIR3
Post hoc	Dependent: ODI score at 1 yr. Independent: as in the preceding analysis but including DD instead of the treatment group, prior disc surgery, and STIR3
Predefined	Dependent: LBP intensity score at 1 yr. Independent: MC1 change (reduced or not reduced), baseline LBP intensity score, age, smoking, body mass index, heavy physical work/lifting
Post hoc	Dependent: LBP intensity score at 1 yr. Independent: as in the preceding analysis plus treatment group, prior disc surgery, and STIR3
Post hoc	Dependent: LBP intensity score at 1 yr. Independent: as in the preceding analysis but including DD instead of the treatment group, prior disc surgery, and STIR3

Table shows analyses predefined in the statistical analysis plan, and analyses performed post hoc after the results of the predefined analyses were available.

STIR 3: most abundant MC edema on STIR, defined in Table 1.

DD indicates disc degeneration; LBP, low back pain; MC, Modic change; MC1, MC type 1; ODI, Oswestry Disability Index; RMDQ, Roland-Morris Disability Questionnaire; STIR, short tau inversion recovery; T1/T2, T1/T2-weighted.

12 to 72 months in patients with MC1 fully converted to MC2 *versus* those with more extensive MC1. Change in MC1 extent was not related to LBP intensity in the study by Jarvinen *et al*.[8] In the population-based study by Tamai *et al*,[28] transformation of MC types was not related to the new incidence of LBP in 3 years, but MC1 was not analyzed separately.

Similar to Mitra *et al*,[16] we found no significant relationship between reduced MC1 and ODI. In contrast, Luoma *et al*[4] and Jarvinen *et al*[8] reported significant

TABLE 3. RMDQ, ODI, and LBP Intensity Scores by Change in MC Edema on STIR After 1 Year (STIR Change) in Subgroup With Edema on STIR at Baseline

	STIR change		
	Reduced	Unchanged	Increased
RMDQ score (0–24), mean ± SD	n = 76	n = 42	n = 31
Baseline	12.5 ± 4.0	12.8 ± 4.6	11.9 ± 4.2
1 yr	9.2 ± 5.7	10.4 ± 6.8	10.2 ± 5.5
Reduction	3.4 ± 5.4	2.5 ± 6.1	1.7 ± 4.3
ODI score (0–100), mean ± SD	n = 75	n = 42	n = 30
Baseline	29.8 ± 9.5	33.7 ± 12.9	31.6 ± 11.5
1 yr	24.6 ± 13.9	30.1 ± 16.8	26.9 ± 14.3
Reduction	5.2 ± 11.6	3.6 ± 13.6	4.7 ± 10.7
LBP intensity score (0–10), mean ± SD	n = 75	n = 42	n = 30
Baseline	6.4 ± 1.3	6.2 ± 1.6	6.3 ± 1.4
1 yr	5.0 ± 2.4	4.9 ± 2.4	5.2 ± 2.2
Reduction	1.4 ± 2.3	1.3 ± 2.4	1.2 ± 1.6

Table shows values for patients with complete data on tabled variables (147–149 of 162 patients).

LBP indicates low back pain; MC, Modic change; ODI, Oswestry Disability Index; RMDQ, Rolland-Morris Disability Questionnaire; STIR, short tau inversion recovery.

TABLE 4. RMDQ, ODI, and LBP Intensity Scores by a Change in MC Edema on T1/T2 Series After 1 Year (MC1 Change) in Subgroup With Edema on T1/T2 (*i.e.*, MC1) at Baseline

	MC1 change		
	Reduced	Unchanged	Increased
RMDQ score (0–24), mean ± SD	n = 61	n = 28	n = 17
Baseline	12.6 ± 4.1	12.3 ± 4.1	12.0 ± 4.4
1 yr	8.4 ± 5.7	10.4 ± 5.8	10.1 ± 6.0
Reduction	4.1 ± 5.6	1.9 ± 5.2	1.9 ± 3.8
ODI score (0–100), mean ± SD	n = 60	n = 28	n = 16
Baseline	29.4 ± 10.5	31.5 ± 11.2	32.5 ± 12.0
1 yr	23.2 ± 13.6	28.2 ± 15.2	30.4 ± 15.8
Reduction	6.2 ± 11.8	3.3 ± 10.7	2.1 ± 12.6
LBP intensity score (0–10), mean ± SD	n = 60	n = 28	n = 17
Baseline	6.5 ± 1.4	6.3 ± 1.1	6.7 ± 0.9
1 yr	4.5 ± 2.5	5.4 ± 2.2	5.7 ± 2.0
Reduction	1.9 ± 2.3	0.9 ± 2.2	1.0 ± 1.7

Table shows values for patients with complete data on tabled variables (104–106 of 116 patients).

LBP indicates low back pain; MC, Modic change; MC1, MC type 1; ODI, Oswestry Disability Index; RMDQ indicates Rolland-Morris Disability Questionnaire; T1/T2, T1/T2-weighted.

relationships (Supplemental File, Table A7, Supplemental Digital Content 8, http://links.lww.com/BRS/C231). Jarvinen *et al*[8] visually estimated MC extent in the percentage of the vertebra, and type 1 part extent in the percentage of the MC, in 5% intervals, using the mean value from hard copies of 3 MRI slices. We used all relevant slices and clinical picture archiving and communication system workstations. In addition, we adjusted for a wider range of potentially relevant factors (age, smoking, body mass index, physical workload, baseline MC edema, prior disc surgery, DD, and treatment group) compared with previous studies[4,8,16] (Supplemental File, Table A7, Supplemental Digital Content 8, http://links.lww.com/BRS/C231).

While reduced MC1 volume in our study was significantly related to LBP intensity but not to the ODI score, changed MC1 extent was related to the ODI score but not LBP intensity in the Jarvinen et al's study.[8] This is difficult to explain. LBP intensity and pain-related disability (ODI) are closely related concepts; therefore, both (as in the Luoma et al's[4] study) or none of them might be expected to be associated with changes in MC1, provided both outcome measures had acceptable responsiveness, which was the case in the AIM study.[30]

Interpretation and Implications

The 95% CIs for the regression coefficients in the predefined final models (Table 5) indicate that the differences between those with and those without reduced MC edema could be a maximum of 3.8 RMDQ points, 7.1 ODI points, and 1.8 LBP intensity points. These extreme values barely exceeded the minimal clinically relevant between-group differences defined in some studies of treatments for LBP (RMDQ: 2.5–4.0 points,[20,31,32] ODI: 7–10 points,[33,34] and LBP intensity: 1.5 points[32]). In addition, reduced edema was weakly correlated with clinical outcomes ($r \leq 0.23$). Thus, our findings do not suggest any associations between reduced MC edema (yes/no) and disability or LBP intensity that are clearly relevant clinically. However, as we cannot rule out a slightly better outcome if edema declines, MC edema remains a relevant factor in further research.

The present findings confirm that a follow-up MRI to assess changes in MC edema is not indicated since the MRI result is unlikely to be clinically useful. However, a follow-up MRI may be indicated when the clinician suspects that the edema is due to spondylodiscitis or malignancy rather than MC.

TABLE 5. Relationship Between Reduced MC Edema and Disability or Pain After 1 Year

		Predefined initial model		Predefined final model		Post hoc model 1		Post hoc model 2	
	*r**	***B* (95% CI)**	***P***	***B* (95% CI)**	***P***	***B* (95% CI)**	***P***	***B* (95% CI)**	***P***
MC edema on STIR (STIR subgroup, n = 162): STIR change (reduced or not = reference) in relation to									
RMDQ (0–24)	0.11	−1.2 (−2.9, 0.5)	0.18	**−1.0 (−2.8, 0.8)**	**0.27**	−1.0 (−2.7, 0.8)	0.28	−1.0 (−2.8, 0.8)	0.27
ODI (0–100)	0.05	−1.8 (−5.7, 2.1)	0.37	−1.4 (−5.4, 2.6)	0.50	−1.3 (−5.3, 2.7)	0.52	−1.4 (−5.4, 2.6)	0.50
LBP intensity (0–10)	0.04	−0.1 (−0.8, 0.6)	0.80	−0.1 (−0.8, 0.7)	0.90	−0.03 (−0.8, 0.7)	0.93	−0.05 (−0.8, 0.7)	0.90
MC edema on T1/T2 (MC1 subgroup, n = 116): MC1 change (reduced or not = reference) in relation to									
RMDQ (0–24)	0.20	−2.0 (−3.9, 0.0)	0.05	**−1.7 (−3.8, 0.3)**	**0.10**	−1.8 (−3.9, 0.2)	0.08	−1.7 (−3.8, 0.3)	0.10
ODI (0–100)	0.14	−3.5 (−7.9, 1.0)	0.13	−2.3 (−7.1, 2.5)	0.34	−2.6 (−7.4, 2.2)	0.29	−2.3 (−7.1, 2.5)	0.34
LBP intensity (0–10)	0.23	−1.0 (−1.8, −0.1)	0.02	−0.9 (−1.8, −0.04)	0.04	−1.0 (−1.9, −0.05)	0.04	−0.9 (−1.8, −0.04)	0.04

**Pearson r for point-biserial correlation between reduced MC edema (yes/no) and reduction in RMDQ, ODI, or LBP intensity score from baseline to 1-year follow-up, based on unadjusted raw data and no imputations.*

Table otherwise shows results from linear regression in 100 imputed data sets with the 1-year RMDQ, ODI, or LBP intensity score as a dependent variable. A predefined initial model is adjusted for the baseline RMDQ, ODI, or LBP intensity score, respectively. The predefined final model is also adjusted for age, smoking (yes/no), body mass index, heavy physical work/lifting (yes/no), and (STIR analysis only) for abundant MC edema on STIR at baseline ("STIR3," yes/no). Post hoc model 1 is further adjusted for prior lumbar disc surgery (yes/no), treatment group (amoxicillin/placebo), and STIR3 (yes/no) at baseline (in both the STIR subgroup and in the MC1 subgroup). Post hoc model 2 is adjusted for disc degeneration (Pfirrmann grade) at baseline in addition to the factors adjusted for in the predefined final model. Results used to assess hypotheses (A) and (B) (see text in the accompanying paper) according to the statistical analysis plan are marked in bold.

B: unstandardized regression coefficient.

MC1 change: change in volume of the type 1 part of MCs on T1/T2 from baseline to one year.

STIR change: change in MC edema on STIR from baseline to 1 year based on volume and intensity of high signal.

STIR3: category of most abundant MC edema on STIR at baseline, defined in the accompanying paper.

LBP indicates low back pain; MC, Modic change; MC1, MC type 1; ODI, Oswestry Disability Index; RMDQ, Rolland-Morris Disability Questionnaire; STIR, short tau inversion recovery; T1/T2, T1/T2-weighted.

Strengths and Limitations

The strengths of this study are the large sample sizes, identical MRI protocols for all patients, MRI evaluations by 3 experienced radiologists, adjustment for possible confounders, and minimal missing data. We did not adjust for spondylolisthesis but excluded patients with symptomatic spondylolistheses. We lacked prestudy data on when the MCs originated compared with symptom start. Our use of previously unvalidated categorical edema change variables was a limitation; however, these variables showed good interrater reliability. Their intrarater reliability was not assessed. We did not quantify the intensity or volume of edema regions, which would have required very time-consuming hand-drawing of regions of interest on all relevant image slices. Thus, we did not report the degree of edema reductions and cannot rule out that marked reductions can be clinically relevant. Despite performing multiple analyses, we maintained the significance level at 0.05 (except for hypothesis "A"). This has been advised for explorative studies[35] but increases the risk of spurious results. Thus, the significant relationship ($P = 0.04$) in the MC1 subgroup requires further support. We analyzed the index levels only, but analyzing all the lumbar levels would not substantially have changed our findings. Based on all levels, edema reductions would be reclassified (from yes to no or no to yes) in only 4 of 162 STIR patients and none of 116 patients with MC1. Finally, our results may not be applicable to patients who have recently undergone spine surgery.

CONCLUSION

After 1 year of follow-up of patients with MCs and chronic LBP, reduced MC edema on MRI was not significantly associated with pain-related disability. There was a weak and probably not clinically relevant association between reduced volume of the type 1 part of MCs and reduced LBP intensity.

➢ Key Points

- ❑ It is not clear from previous research whether or not reduced MC edema over time on MRI is accompanied by improved clinical outcomes in patients with chronic LBP.
- ❑ After 1 year in this study, neither reduced MC edema on STIR nor reduced MC edema on the T1/T2 series was significantly associated with pain-related disability.
- ❑ Reduced MC edema in the T1/T2 series (i.e., reduced volume of the type 1 part of MCs, yes or no) was significantly related to reduced LBP intensity, but unlikely to be clinically relevant.

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