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ORIGINAL ARTICLE

Probiotics for chronic low back pain with type 1 Modic changes: a randomized double-blind, placebo-controlled trial with 1-year follow-up using *Lactobacillus Rhamnosis GG*

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Abstract

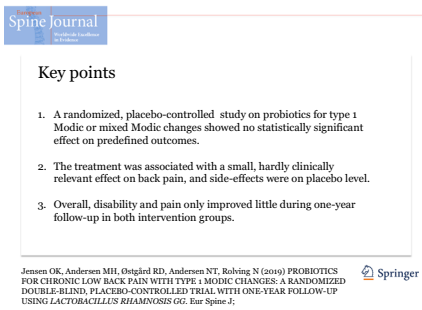
Purpose To investigate whether treatment by lactic acid bacteria for 100 days is associated with change of disability and pain in chronic low back pain (CLBP) patients with type 1 or mixed Modic changes (MC) during 1-year follow-up.

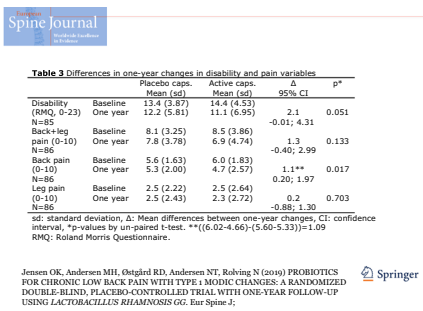
Methods Eighty-nine patients with CLBP and type 1 MC or mixed MC were randomized to receive either one capsule *Lactobacillus Rhamnosis GG* (6 billion colony-forming unit per capsule) twice daily or placebo capsules for 100 days.

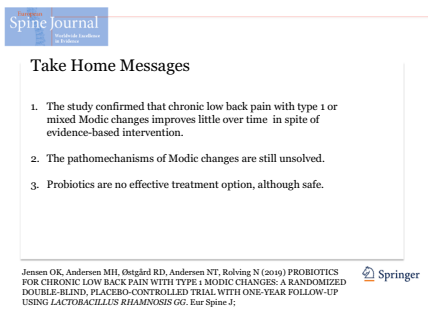
Results Missing values at 1 year were 4% and 3% in the disability and pain variables, respectively. The predefined outcomes disability and back + leg pain only changed little during follow-up with no statistically significant differences between groups. At 1 year, back pain had on average decreased by 1.1 more on a 0–10 scale (95% confidence interval 0.20–1.97) in the group treated by lactic acid bacteria than in the control group. There were no differences regarding other predefined outcomes, i.e. global effect or percentage with minimal disability at 1 year. Nine per cent of the patients reported gastrointestinal side effects without difference between groups.

Conclusions No differences were found regarding the predefined outcomes. Overall, there was little improvement during the 1-year observation period. A small, though hardly clinically relevant, effect on back pain was seen after treatment by *Lactobacillus Rhamnosis GG*, and the treatment was without side effects in comparison with the control group.

Graphic abstract







Keywords Modic changes · Chronic low back pain · Probiotics · Lactic acid bacteria · Inflammation · Vertebral end-plate oedema

Introduction

Low back pain (LBP) is the leading cause of disability in the world [1]. As yet, there are no effective treatments for chronic LBP (CLBP) [2, 3] that account for most of the LBP disability [4]. Modic changes (MC) have been shown to be a risk factor

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for troublesome CLBP [5], especially type 1 Modic changes [6].

MC is classified as type 1, 2, and 3, the latter being rare. Classification has been based on magnetic resonance imaging (MRI) [7]. MRI of type 1 changes (MC1) displays a low T1-weighted signal and a high T2-weighted signal. Type 2 changes (MC2) appear with high signal and type 3 changes (MC3) with low signal in both sequences, respectively. In the so-called mixed type, both MC1 and MC2 are present in the same lesion [8]. Histology of the endplates in MC1 shows fissures and granulation tissue in combination with oedema extending into the associated bone marrow [9]. An increased number of TNF-immunoreactive cells have been identified in the vertebral endplates from patients with MC1 and MC2, and more TNF-immunoreactive cells have been identified in MC1 as compared to MC2 [10].

There is no general agreement about the cause of inflammation in MC1 [11]. A hypothesis of latent infection with Proprionibacterium Acnes has been suggested, after a randomized controlled trial by Albert et al. [12] comparing broad-spectrum antibiotic with placebo showed effect. These findings have been confirmed by Mohanned et al. [13], although their study unfortunately had a high drop-out rate and no long-term follow-up. Furthermore, in a rat disc model, MC1 like changes was demonstrated histologically and by MRI following inoculation with Proprionibacterium Acnes that had been isolated from a human L4-5 disc with MC1 changes [14].

Autoimmunity has been suggested as another possible cause of inflammation. A later study by the same research group [15]—also using a rat disc model—showed that in case of end-plate defects, bone marrow cells can start an autoimmune process when subjected to nucleus pulposus cells resulting in a histologic picture similar to MC1 lesions. Furthermore, MRI's of the discs displayed MC1 similar changes.

Because of the late-onset effect of antibiotic treatment in Albert et al.'s study, we have hypothesized that the antibiotic effect could be caused by a change of the gut microbiota, the commensal bacteria in the gut, inducing a change in the immune system, and not a direct effect on a hypothesized infection. Thus, the aim of the present double-blinded placebo-controlled study was to investigate whether treatment by lactic acid bacteria for 100 days was associated with change of disability and pain in CLBP-patients with MC1 or mixed MC during 1-year follow-up.

Methods

Hypothesis

Treatment by lactic acid bacteria for 100 days is associated with increased improvement in disability and pain in a group of CLBP-patients with MC1 or mixed MC during 1-year follow-up as compared to a placebo control group.

Study design

Randomized (1:1) single-centre, double-blind, placebo-controlled parallel-group trial with 1-year follow-up.

Eligibility criteria

Inclusion criteria: Referral from one of the two spine centres in the Central Region Denmark (Silkeborg or Aarhus); ability to speak and understand Danish; age 18–65 years; MRI verified MC1 (or mixed MC) within the last 3 months; no sign of activation of the immune system at inclusion (C-Reactive Protein (CRP) within reference intervals); back pain dominating over leg pain; back pain duration > 3 months; moderate disability (Roland Morris Questionnaire > 5).

Exclusion criteria: Intended or planned back surgery; back surgery for herniated discs or spinal stenosis within the last 6 months; previous fusion surgery; planned treatment by antibiotics for MC; treatment by antibiotics for MC within the last 6 months; more than 2 weeks antibiotic treatment within the last 3 months; current treatment by immunosuppressants; inability to enter or complete the project because of psychological, social or geographic reasons; known intestinal pathology; autoimmune disease; immune deficiency; malabsorption; cancer or chronic infection.

Comment

No patients were recruited from Aarhus Spine Centre.

Setting and patients

Ninety-four patients with CLBP and MC1 or mixed MC were recruited from the Spine Center, Silkeborg Regional Hospital (Fig. 1) to the Research Unit (RU), which is part of the Spine Center. MRI of the lumbar spine usually was available at the patients' first visit at the Spine Center. If not, MRI would be ordered subsequently. The first part of the intervention was similar for both patient groups as described below:

LBP treatment as usual in the Spine Center was provided by a rheumatologist or a physiotherapist, and usually by both, including recording of LBP history, clinical low back examination, information on what LBP is, and which type of LBP is present, advice of being active, information of exercise being the best treatment except in few cases where surgery might be an option. If in doubt, the case was discussed with spine surgeons at weekly conferences. The patients were tested and advised by a physiotherapist regarding specific exercises or general exercise. If MRI of the lumbar

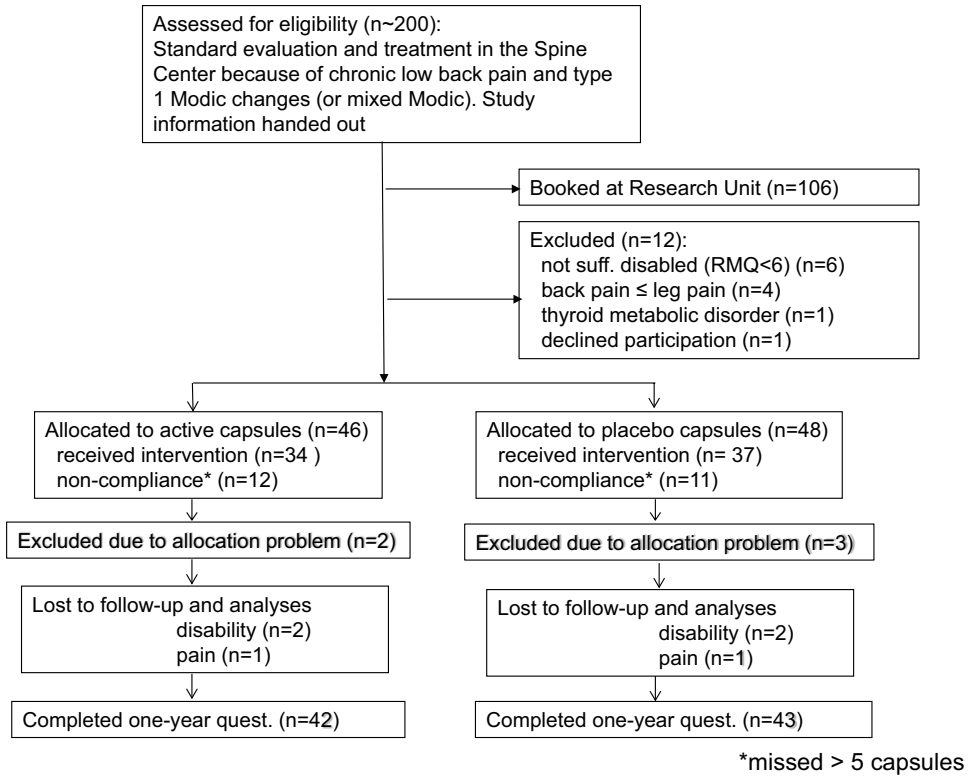

Fig. 1 Flow chart

spine showed MC1 or mixed MC and no contraindications for participation were present preliminarily, the patients were informed about the "Modic Project" and participation information with a phone number was handed out, making it possible for the patient to get in touch with the secretary of the RU. Patients calling back because of interest in participation were booked for a visit. At this visit, the participation information was discussed with the patient, and uncertainties were clarified. If the patient was still interested in participation, the recording of LBP history and low back examination were repeated, and the LBP information was again offered to the patient in summary. The patients were informed that MC1 may cause long-lasting pain and limitations in daily life but is not dangerous. The rheumatologist prescribed supplemental pain medicine following guidelines if considered necessary. Inclusion and exclusion criteria were examined, except the CRP-criteria awaiting the result of the subsequent blood sample. In the meantime, the patient was again tested and instructed by the RU-physiotherapist to ensure similar information and instruction in exercises. The patients were instructed to complete an exercise diary, and a follow-up visit with the physiotherapist was arranged after 2 weeks.

If there were no exclusion criteria and all inclusion criteria were met, a consent form was signed and randomization was performed. Trial medication was handed out to the patients, and follow-up was planned at 2 weeks, 101 days, 6 months (by telephone), and 1 year. At the follow-up visit with the physiotherapist at 2 weeks, the exercise programme was adjusted if necessary, and supervised exercise was prescribed when considered relevant. The patients were informed that they could get in contact with the RU when needed during follow-up, and they were told about the possibility of surgical evaluation in case of deterioration or symptoms indicating radiculopathy. If the patient was on sick leave, then he or she was advised to resume work when possible.

Interventions

Active group: Probiotic Dicoflor ® twice daily for 100 days. Each capsule contains 6 billion *Lactobacillus Rhamnosis GG.*

Placebo group Placebo capsules indistinguishable from Dicoflor twice daily for 100 days.

Both active capsules and placebo capsules were provided by the Pharmaceutical Company (Pharmaforce ApS) and were kept on two different shelves in a refrigerator in similar boxes except from two different identification codes. Only one of the authors (NR) was aware of the coding in case of serious side effects occurring.

Measures

Age and sex were derived from the CPR number (the Danish social security number). Pain duration, smoking habits, and sick-listing data were registered by the baseline

questionnaire. Sick-listing was registered at baseline and after 1 year as a yes/no answer on the question: Are you sick-listed? Global effect was measured by the 1-year questionnaire by asking the patient to tick a box on a five-point Likert scale. Side effects were registered at the end of the intervention period by the open question: Have you experienced any side effects due to the treatment?

Body mass and height were measured and body mass index (BMI) calculated as usual.

Disability in daily life activities: A validated Danish version of the Roland Morris Questionnaire (RMQ) including 23 items [16], summing up to a total score of 0–23 points (best–worst).

Back + leg pain by the LBP rating scale: This scale has previously been validated [17] and comprises a sum score for back and leg pain, respectively, based on three questions about worst, average, and actual pain during the preceding 2 weeks. Thus, the patient indicates on a 11 point NRS (0–10 points), their worst, average and actual pain for back pain and for leg pain, giving six scores in total, adding up to a total sumscore of 0–60 (best–worst), 0–30 for back pain and leg pain, respectively.

Outcomes

Primary outcome: Difference between groups in change in disability (RMQ) from baseline to 1 year.

Secondary outcomes: Differences between groups in changes in back + leg pain from baseline to 1 year; the percentages of patients in each group with minimal disability (RMQ < 4) at 1 year; patient-reported global effect in each group; and sick leave.

Since the patients were selected by having more back pain than leg pain, it was also chosen to perform a secondary analysis for the difference between groups in change in back pain from baseline to 1 year.

Sample size

Power calculation was based on the results of the study by Albert et al. [12] with the assumption that treatment by probiotics would be less effective as compared to the effect shown in Albert et al's study. The change in disability in each treatment group in their study was 8 and 1, respectively. We assumed that the standard deviations were similar (6.5), and the sample size was calculated on the assumption that the disability changes would be 8 and 5, respectively. A difference of 3 in RMQ-score would make a minimal important change probable, i.e. reduction of disability by at least 30% compared to baseline [18]. Furthermore, we assumed a drop-out rate of 10% resulting in a sample size of 94 patients. This number was achieved; however, the last five patients were excluded, please see below.

Randomization

Study data were collected and managed using REDCap electronic data capture tools hosted at Aarhus University. Unstratified random allocation lists were generated to support the two treatment groups at a 1:1 ratio by the method of permutated block randomization with random varying block-sizes of 4, 6, and 8. The random allocation list was generated and uploaded to REDCap by an independent service provider (Clinical Trial Unit, Dept. of Clinical Medicine, Aarhus University) maintaining proper concealment of randomization.

Due to an unfortunate mistake at the end of the inclusion period, a few patients may not have received the allocated capsules: Before inclusion of the last five patients, there were only capsules for one patient left on one of the shelves at the RU. The company informed us that they had no more placebo capsules. Additional active capsules with a new batch number were sent. Therefore, these five patients have been excluded from the study, and the mistake was reported to the Ethics Committee.

Ethical approval

All participants provided written informed consent. The study was approved by The Danish Data Protection Agency (1-16-02-9-16) and by The Central Denmark Region Committees on Health Research Ethics (1-10-72-308-15). The trial was registered at ClinicalTrials.gov (NCT03100266).

Data analyses

The subscales for back pain and leg pain were transformed to a 0–10 NRS scale by dividing all scores by 3. Baseline measures in the two intervention groups were compared by Chi-square tests and Wilcoxon/Mann–Whitney rank-sum tests. Differences between groups in changes in disability and back + leg pain, respectively, were analysed by unpaired *t* tests assuming that all patients had received treatment as planned (intention to treat). Afterwards, differences between groups in back pain and leg pain were analysed separately in the same way. The relevant variables were checked by normality plots to ensure appropriate use of the *t* tests.

The number of patients in each group with minimal disability (RMQ < 4) at 1 year was compared using Chi-square test. Patient-reported global effect was tested using Wilcoxon/Mann–Whitney rank-sum test. In each group, the change in proportion of sick-listed between baseline and 1 year was estimated as the difference in paired proportions, and these differences were compared between groups by a standard *z* test. The analyses were performed using the statistical package STATA 15 [19], and a significance level of 5%, two-sided, was chosen.

Results

A specialist of radiology confirmed that MRI of the lumbar spines from all patients showed MC1 or mixed Modic changes at one or more levels. Missing values at 1 year were few (disability: 4%, pain: 3%).

The compliance was good: 57 patients took all capsules as described, 10 patients missed one capsule, 9 patients missed 2–10 capsules, 12 patients missed 10–20 capsules, and 6 patients missed more than 20 capsules (Fig. 1). One patient sought treatment by antibiotics at a "Modic clinic" after the treatment period and continued with project capsules afterwards throughout the follow-up period.

Baseline variables are shown in Table 1. There were only minor differences between the two groups.

The scores for all measures changed little during the 1-year follow-up (Table 2). The mean disability score for the 89 patients completing the 1-year questionnaire was reduced from 13.9 to 11.6 (17%) and for back + leg pain from 8.3 to 7.4 (11%). During the first 100 days, the mean values of changes in disability were almost identical in the two groups, but afterwards the differences increased in favour of the active group, although not reaching statistical significance at 1 year (Tables 2 and 3). The pattern was similar in regard to back + leg pain (Tables 2 and 3).

There were no statistically significant differences between the two groups regarding the predefined primary or secondary outcomes, i.e. changes in disability and back + leg pain (Table 3). Likewise, there were no differences between the number of patients reporting global effect of treatment (Table 4) or reporting of minimal disability, RMQ < 4 (8 of 42 in the active group vs. 3 of 43 in the placebo group, $p = 0.097$), at 1 year.

Fifteen of the patients sick-listed at baseline had returned to work at 1 year, 9 out of 15 patients in the placebo group and 6 out of 11 in the active group (8 missing at 1 year). The proportion of sick-listed decreased in the placebo group by 0.20 (95%CI 0.06; 0.35, $p = 0.004$) and in the active group by 0.08 (95%CI − 0.10; 0.25, $p = 0.51$). These proportions were not statistically significantly different, $p = 0.27$.

On a 0–10 scale, back pain decreased by 1.1 more (95% CI: 0.20–1.97, $p = 0.017$) in the active group than in the control group (Table 3). The corresponding improvement was 22% ((6 − 4.7)/6) and 7% ((5.6 − 5.2)/5.6) in the active and placebo group, respectively, which is less than minimal important change (30%). Leg pain reporting was low (mean < 3) with larger standard deviations, and the decrease in leg pain was very small with no differences between the intervention groups (Table 3).

Gastrointestinal side effects were reported seldom, i.e. by four patients in each group corresponding to 9%. No other side effects were reported except from two patients in the placebo group reporting non-specific symptoms as tired arms or headache. Other health-related episodes during follow-up not related to the project were as follows: Two patients were referred for surgery and had fusion surgery. One patient with increasing hip pain had hip arthroplasty. One patient was operated for colon cancer, and another patient was operated for gut fistulas (the patient also reported previous episodes).

Table 1 Baseline variables

	Placebo capsules $n = 45$	Active capsules $n = 44$
Sex, women, *n* (%)	34 (75.7)	32 (72.7)
Age, mean (sd)	46.3 (10.7)	46.1 (9.0)
BMI (kg/m^2), mean (sd)	25.9 (3.97)	26.0 (3.80)
Disability (RMQ:0–23), mean (sd)	13.6 (3.98)	14.4 (4.60)
Back + leg pain (0–10), mean (sd)	8.4 (3.44)	8.6 (3.85)
Back pain (0–10), mean (sd)	5.7 (1.67)	6.0 (1.81)
Leg pain (0–10), mean (sd)	2.7 (2.31)	2.6 (2.65)
Pain duration, n (%)		
2–3 months	1 (2)	2 (4)
3–6 months	5 (11)	2 (4)
7–12 month	8 (18)	7 (15)
> 1 year	31 (69)	33 (76)
On sick leave, *n* (%)	16 (36.3)	12 (27.3)
Smoking, *n* (%)		
Daily or intermittent	10 (23)	14 (31)
Previous	15 (33)	13 (30)
Never	20 (44)	17 (39)

RMQ Roland Morris Questionnaire

Differences between groups were tested by chi-square and rank-sum tests

All *p* values were > 0.35

Discussion

This randomized controlled study showed no differences between intervention groups in regard to the predefined outcomes disability, back + leg pain, patient-reported global effect or the number of the patients with minimal disability at 1 year. However, back pain decreased a little more in the active intervention group than in the control group as described below.

The study confirmed that treatment with probiotics, as used here, was safe and implicated no more side effects than placebo. The study also confirmed that CLBP with MC1 is a grave back pain disorder with little tendency to

Table 2 Disability, back + leg pain, back pain and leg pain during follow-up

	Baseline Mean (sd) *n*	2 weeks Mean (sd) *n*	100 days Mean (sd) *n*	6 months Mean (sd) *n*	1 year Mean (sd) *n*
Disability					
Placebo	13.6 (3.98) 45	12.5 (4.50) 45	11.8 (5.52) 45	12.0 (5.93) 44	12.2 (5.81) 43
Active	14.4 (4.60) 44	13.0 (4.84) 43	11.9 (5.92) 43	11.4 (6.08) 43	11.1 (6.95) 42
*Back + leg pain**					
Placebo	8.4 (3.44) 45	7.6 (3.14) 45	7.4 (3.93) 45	7.9 (3.60) 44	7.8 (3.78) 43
Active	8.6 (3.85) 44	8.4 (3.64) 43	7.2 (4.05) 43	7.4 (4.28) 43	6.9 (4.74) 43
*Back pain**					
Placebo	5.7 (1.67) 45	5.3 (1.70) 45	5.1 (2.09) 45	5.4 (2.00) 44	5.3 (2.00) 43
Active	6.0 (1.81) 44	5.9 (1.68) 43	5.2 (2.19) 43	4.9 (2.26) 43	4.7 (2.57) 43
*Leg pain**					
Placebo	2.7 (2.31) 45	2.3 (2.03) 45	2.3 (2.43) 45	2.4 (2.41) 44	2.5 (2.43) 43
Active	2.6 (2.65) 44	2.5 (2.50) 43	2.1 (2.54) 43	2.5 (2.65) 43	2.3 (2.72) 43

Disability measured by Roland Morris Questionnaire

*Transformed to VAS (0–10)

Table 3 Differences in 1-year changes in disability and pain variables

		Placebo caps. Mean (sd)	Active caps. Mean (sd)	Δ 95% CI	*p**
Disability (RMQ, 0–23) *N* = 85	Baseline	13.4 (3.87)	14.4 (4.53)		
	1 year	12.2 (5.81)	11.1 (6.95)	2.1 − 0.01; 4.31	0.051
Back + leg pain (0–10) *N* = 86	Baseline	8.1 (3.25)	8.5 (3.86)		
	1 year	7.8 (3.78)	6.9 (4.74)	1.3 − 0.40; 2.99	0.133
Back pain (0–10) *N* = 86	Baseline	5.6 (1.63)	6.0 (1.83)		
	1 year	5.3 (2.00)	4.7 (2.57)	1.1** 0.20; 1.97	0.017
Leg pain (0–10) *N* = 86	Baseline	2.5 (2.22)	2.5 (2.64)		
	1 year	2.5 (2.43)	2.3 (2.72)	0.2 − 0.88; 1.30	0.703

sd standard deviation, Δ Mean differences between 1-year changes, *CI* confidence interval, *RMQ* Roland Morris Questionnaire

**p* values by unpaired *t* test

**((6.02 − 4.66) − (5.60 − 5.33)) = 1.09

improvement. During follow-up, disability of the whole cohort was reduced by just 17% in spite of active back pain management. Only 13% of the patients reported minimal disability at 1 year. Furthermore, back + leg pain was reduced by just 11% at 1 year. This was far from 30% recommended as a minimal important change [18].

The lack of improvement over time in MC1 patients has been supported by other studies: Sick-listed LBP patients with MC1 did not improve during 1 year in contrast to other patients, including MC2 patients, who also improved [20]. Furthermore, in the control group of Albert et al.´s study and in another study comparing MC1 and MC2 patients,

Table 4 Patient-reported global effect at 1 year

	Placebo capsules	Active capsules	All
Excellent	2	2	4
Good	3	6	9
Moderate	14	10	24
No effect	20	24	44
Negative effect	4	1	5
Total	43	43	86

$p = 0.676$ (Rank-sum test)

disability and pain changed minimally during 1 year in MC1 patients [12, 21]. In addition, in a cross-sectional study including only persons < 50 year, MC1 was associated with pain, whereas MC2 was not [6].

Back pain is the main complaint in these patients and was part of the secondary outcome back + leg pain. At 1 year, the difference in back pain across groups was 1.1 points on a 0–10 scale corresponding to 7% and 22% improvement in the placebo and active group, respectively. Although statistically significantly better, the improvement in the active group did not reach the 30% defined as minimal important change. It may also be a coincidental finding as back pain was not defined as secondary outcome on beforehand, and the primary outcome was not statistically significantly different, although deviating in the same direction.

In Albert et al.'s study [12], 1-year improvement in back pain and disability were 45% and 53%, respectively, in the group treated with broad-spectrum antibiotics for 100 days. Some of that change, however, may have been caused by a spontaneous improvement in back pain owing to a decrease in radicular pain in the intervention group, as leg pain, initially being high at median 5.3 in their study, improved even more than back pain to a median 1.7 (68% reduction). In the control group, leg pain was lower (median 4.0) and tended to increase during follow-up. In the present study, leg pain intensity, measured by the same questionnaire as in Albert et al.'s study, was considerably lower (mean < 3) since our patients were selected by having less leg pain intensity than back pain intensity, and leg pain improved very little during follow-up with no differences between groups.

Current consensus of the pathology considers the cause of inflammation in MC to be infectious or autoimmune [11]. As yet, there is no final evidence for either of these mechanisms, and the results of the present study were not conclusive.

The immune system may be linked to disturbances of the gut microbiome. Under normal conditions the host and the gut microbiome live in homoeostasis; however, alterations in the microbiota (dysbiosis) may induce mucosal inflammation which also can elicit changes of the immune system at distant sites [22].

Autoimmune inflammatory disorders have been shown to be related to disturbances of the gut microbiome, in particular rheumatoid arthritis and psoriatic arthritis [23]. Probiotic treatment has been shown to be able to reduce the concentrations of the proinflammatory cytokines TNF-α, IL-6 and L-12 and to increase the regulatory cytokine IL-10 [24]. MC1 is also an inflammatory, and possibly an autoimmune, disorder as described previously. We have hypothesized that the effect seen in Albert et al.'s study was owing to a change of the gut microbiota and not a direct effect of antibiotics on bacteria. However, the results of the present study were too weak to give substantial support to the autoimmune hypothesis.

Other treatment options for MC may include zoledronic acid or denosumab with documentation for a small short-time effect on pain (6 months). Numerous side effects were reported, and there was no effect on disability [25]. Effects of glucocorticoid injection and fusion surgery have been reported, but no controlled studies have been published on these issues [11].

Strengths

The study has several strengths. The double-blinded design with low drop-out rate minimizes the risk of bias, and furthermore, compliance was acceptable and side effects at placebo level. The lack of differences between the two intervention groups during the first 100 days points to adequate blinding of caretakers and patients. The company providing the capsules for this study had no influence on protocol, statistical analyses or writing.

Limitations

Back pain was not predefined as secondary outcome, because back + leg pain has been documented as an important prognostic factor in previous studies [26, 27]. Retrospectively, this was not an appropriate decision, since the present sample of patients was selected by having less leg pain than back pain.

The problems regarding allocation of the right capsules to the last five patients may be viewed as a limitation of the study, but seeing we had a very high follow-up rate of the remaining 89 patients, we believe it has affected our conclusion little. These problems have been reported to the Central Denmark Region Committees on Health Research Ethics. They had no further comments since the possible fault has had no potential of causing negative consequences for the patients.

Perspectives

If performing similar studies in the future, it is recommended to collect faecal samples in order to study whether a 3 months treatment period by probiotics can alter the gut microbiota. Furthermore, it is recommended to consider higher doses or longer treatment periods by probiotics. Other probiotics, including yoghurt products, may be tested in future studies. However, the present results do not allow any conclusion regarding other lactobacillus products.

Conclusions

Overall, there was no effect of 100 days treatment with probiotics except for a small, hardly clinically relevant effect on back pain at 1 year. The study confirmed that CLBP with MC1 or mixed MC is a grave disorder improving little over time.

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Compliance with ethical standards

Conflict of interest Ole Kudsk Jensen, Morten Hovgaard Andersen, René Drage Østgård, Niels Trolle Andersen and Nanna Rolving declare that they have no conflict of interest.

Ethical approval Ethics approval was obtained from the institutional review board before commencement of this study. No benefits in any form have been or will be received from any commercial party related directly or indirectly to the subject of this manuscript.

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