Middle education	88 (28.2)
Higher education	158 (50.6)
Number of affected joint sites, mean (sd)	5.5 (2.3)
Duration of OA symptoms	-
6 months – 1 year	2 (0.6)
1 – 5 years	29 (9.3)
5 – 10 years	56 (17.9)
> 10 years	225 (72.1)
Age first complaints	-
< 25 years	32 (10.3)
25 – 35 years	50 (16.0)
35 – 45 years	85 (27.2)
45 – 55 years	94 (30.1)
55 – 65 years	40 (12.8)
> 65 years	11 (3.5)
SF-36 subscales, mean (sd)	-
Physical functioning	47.8 (22.0)
Physical role limitations	28.4 (36.9)
Bodily pain	45.7 (19.4)
General health	45.1 (20.0)
Vitality	48.1 (19.5)
Social functioning	60.7 (25.7)
Emotional role limitations	67.6 (42.0)
Mental health	72.8 (16.1)

Osteoarthritis and Cartilage

* sd = standard deviation

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COMPARATIVE EFFECTIVENESS OF DIFFERENT PLACEBOS AND COMPARATOR GROUPS FOR HAND OSTEOARTHRITIS EXPLORING THE IMPACT OF CONTEXTUAL FACTORS: A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED TRIALS

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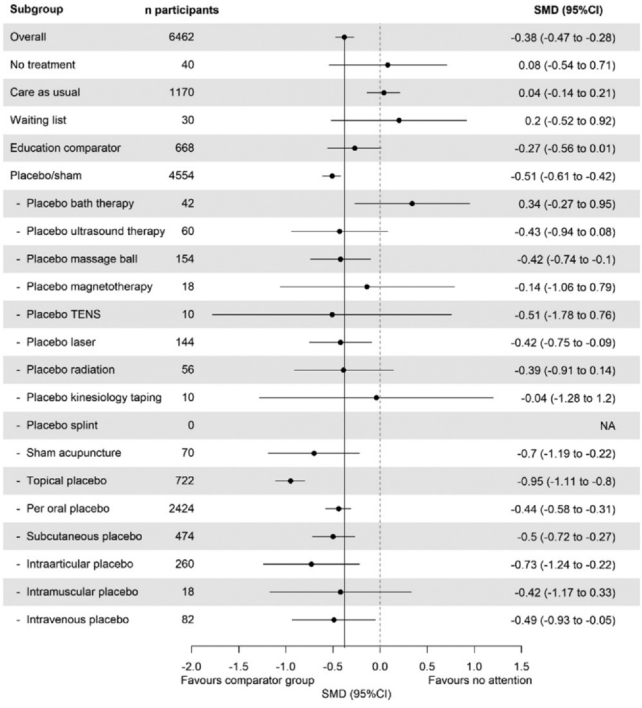
Purpose (the aim of the study): To examine the pain relief effects of different placebos/comparators over a matched null-arm in randomized hand osteoarthritis trials, and the impact of contextual factors.

Methods: We systematically searched PubMed, EMBASE and CENTRAL from inception to December 26, 2021. We included randomized controlled trials of people with hand OA with a placebo or an untreated control group. We assessed the Risk of Bias with Cochrane Risk-of-Bias tool version 2. The placebo/comparator response (i.e., the contextual effect) for each trial was compared with a matched null-arm as contrast. This counterfactual null-effects approach was manually imputed as having an average zero change from baseline, with the same standard deviation (SD) as collected for the actual comparator group. We used a standard random effects meta-analysis to combine the estimated standardized mean differences. The effect of the contextual factors was examined in meta-regression and stratified models with pain as the dependent variable. The study was prospectively registered at the International Prospective Register of Systematic Reviews (PROSPERO; CRD42022298984).

Results: 84 trials (7,262 participants) were eligible for quantitative synthesis, of which 76 (6,462 participants) were eligible for the stratified analyses. Placebos were superior to the matched null-arm in improving pain with an effect size (SMD; standardized mean difference) of -0.51 (95 % confidence interval -0.61 to -0.42), while other comparators were not. See the **Figure** showing the pain relief effect of the different placebos/comparators over the matched null-arm. When analyzing all comparators the contextual factors open-label trial design and overall risk of bias explained some of the between-trial variation. Blinded trial designs were associated with a higher placebo response for pain compared to an open-label trial design with SMD -0.51 (-0.62 to -0.41) and -0.10 (-0.24 to 0.05), respectively. Low risk of bias was associated with a higher placebo response for pain compared to some concern or high risk of bias with SMD of -0.65 (-0.90 to -0.40), -0.39 (-0.54 to -0.24), and -0.30 (-0.42 to -0.17), respectively.

Conclusions: Placebos were superior to a matched null-arm, while other comparators were not. The contextual effect evaluated according to pain for people with hand osteoarthritis was increased by appropriate blinding and also reflected better placebo response in lower risk of bias assessment. Results emphasize the importance of using appropriate comparators in clinical trials.



Comparative effectiveness of comparators for pain illustrated by their stratified subgroups.

Forest plot showing the comparative effectiveness of the comparator groups. The solid line indicates the overall effect of all groups. The dashed line equals an effect size of zero, with comparator groups crossing this line showing no effect.

SMD = standardized mean difference, TENS = transcutaneous electrical nerve stimulation, NA = not available, CI = confidence intervals. No pain data was available for the placebo splint subgroup.

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CONVENIENT OPTIONS IN THE MANAGEMENT OF OSTEOARTHRITIS: EFFECT OF BACILLUS PROBIOTICS VS. BIOACTIVE CONCENTRATE FROM SMALL SEA FISH

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Purpose (the aim of the study): The effectiveness and safety of bioactive fish concentrate in treatment of musculoskeletal diseases has been proven in the different studies. The bioactive fish concentrate contains hyaluronic acid, chondroitin sulfate, keratan sulfate, dermatan sulfate,

free amino acids, macro- and microelements and has analgetic, antiinflammation and structurally modifying effects. Therefore, bioactive fish concentrate is used as symptomatic slow acting drugs for osteoarthritis (OA) therapy.

The research of colon dysbiosis in the progression of OA and the use of probiotics in the combined treatment of OA are actually. The creation of multicomponent probiotics compositions is one of the most promising ways to optimize the positive action of the genus Bacillus and avoid their side effects.

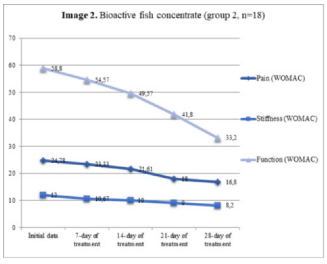
The aim of the study was to investigate the effectiveness of administration of Bacillus genus composition in treatment of OA with bioactive fish concentrate.

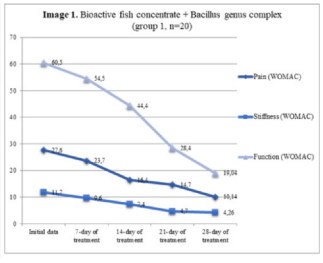
Methods: 38 patients with knee OA grade II were enrolled in the study. Bacillus genus complex (*B. Subtilis, B. licheniformis*, *B. amyloliquefaciens*, *B. megaterium*, *B. pumilus*) $1.7*10^9$ daily orally was appointed with bioactive fish concentrate 2.0 in a day intramuscularly, for 28 days were administered for treating OA (group 1, n=20). Bioactive fish concentrate in monotherapy 2.0 in a day intramuscularly, for 28 days was used for comparison (group 2, n=18). Treatment efficacy was monitored using Western Ontario McMaster Osteoarthritis Index (WOMAC). WOMAC subscales scores were transformed to a 0-100 scale: a WOMAC score of 0 indicates that the patient has no problems and a score of 100 indicates that the patient has extreme difficulty. A score of 75 indicates that a patient has severe difficulty, 50 indicates moderate difficulty, and 25 – mild. The assessment of WOMAC subscales (pain, stiffness, function) was carried out after the summation of the points for all questions and is presented in the form of average values.

Results: The averaged results of WOMAC subscales are presented in Image 1 and Image 2. In the group 1 we detected the faster achievement of significant clinical effect. The decrease of pain by 40.60 % ($p < 0.05$), stiffness by 36.75 % ($p < 0.05$) and improvement of knee function by 26,61 ($p < 0.05$) were observed on the 14-day of treatment. In the group 2 the decrease of pain by 27.36 % ($p < 0.05$), stiffness by 25.0 ($p < 0.05$) and improvement of joint function by 28.9 % ($p < 0.05$) were observed on the 21-day of the therapy.

After 28 days of treatment, in the group 1 we detected the decrease of pain by 62.31 % ($p < 0.05$), stiffness by 63.59 % ($p < 0.05$) and improvement of joint function by 68.52 % ($p < 0.05$). The group 2 was demonstrated the decrease of pain by 32.32 % ($p < 0.05$), stiffness by 31.67 % ($p < 0.05$) and improvement of joint function by 43.53 % ($p < 0.05$) compare to initial data. The final averaged results of WOMAC subscales in the group 1 had the significant better results in compare to group 2 and demonstrated the more effectiveness.

Conclusions: Application of the Bacillus genus complex in the management of knee OA grade II with bioactive fish concentrate leads to faster achievement of significant clinical effects compare to monotherapy with the bioactive fish concentrate only (the significant decrease of pain, stiffness, improve of joint function - on the 14-day of treatment). Combination therapy of OA with bioactive fish concentrate and Bacillus genus complex demonstrates the significant more effectiveness after 28-day of treatment comparing to the monotherapy.





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THE ADDITIONAL VALUE OF RADIOGRAPHIC OSTEOARTHRITIS FOR THE PREDICTION OF PERSISTENT ANKLE COMPLAINTS IS NEGLIGIBLE

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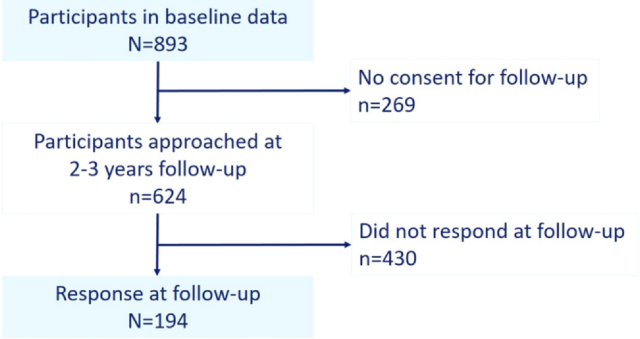
Purpose (the aim of the study): Ankle complaints often persist for years and are a common reason for medical consultation. Medical aid for patients with ankle complaints could be better targeted if we could predict in which patients ankle complaints will persist. In a population referred for ankle radiography, the prevalence of radiographic osteoarthritis (OA) is substantial, but its additional predictive value for persistent complaints is unknown. Therefore, we examined the prognosis of complaints 2-3 years after referral for ankle radiography by any physician, assessed clinical prognostic factors and the additional predictive value of radiographic OA for persistent ankle complaints.

Methods: Of 893 adults referred for ankle radiography of the original cross-sectional study, 624 provided consent for follow-up measurements (Figure 1). At baseline participants completed paper questionnaires in the waiting room and X-rays were scored for radiographic OA. After 2-3 years participants completed a follow-up questionnaire including persistent ankle complaints. The primary outcome persistent complaints after 2-3 years was determined using the Global Rating of Change Scale, categorized into persistent complaints i.e. 'slightly improved' – 'worse than ever' (score 3-7) and no persistent complaints, i.e., 'completely recovered' – 'strongly improved' (score 1-2). Candidate prognostic factors at baseline were selected based on previous literature: age, sex, body mass index (BMI), predominant symptoms (stiffness (yes/no) and functional loss (yes/no)), pain during activity (NRS-11) and referral for chronic ankle complaints (≥12 weeks without or with an ankle trauma ≥12 weeks before examination). To assess prognostic factors for persistent complaints after 2-3 years, logistic regression analysis was used with backward selection of variables until a model was reached with only p-values < 0.2. To evaluate the discriminative ability of the prediction models for persistent complaints, the area under the curves (AUCs) and corresponding 95% CIs of the models with and without radiographic OA were calculated.

Results: Ankle complaints persisted in 71 (36.6%) of the 194/624 (31.3%) responders at 2-3 years follow-up. The responders were on average older, more often women, and reported at baseline more often a previous trauma and slightly lower levels of pain (NRS, ankle osteoarthritis scale (AOS)) and disability (AOS) than non-responders. BMI (OR 1.08; 95% CI 1.01-1.15), stiffness as predominant symptom (OR 1.69; 95% CI 0.89-3.21), and referral for chronic complaints (OR 2.84; 95% CI 1.45-5.57) were included in the initial model for predicting persistent complaints (AUC=0.69; 95% CI 0.60-0.76) (Table 1). After adding radiographic OA (OR 2.36; 95% CI 1.01-5.50), the AUC of the final model became 0.70; 95% CI 0.61-0.77).

Conclusions: Ankle complaints persist in a considerable proportion of patients 2-3 years after referral for ankle radiography. At the time of ankle radiography, a higher BMI, referral for chronic ankle complaints and presence of radiographic OA are associated with persistent ankle complaints 2-3 years later. However, to determine radiographic ankle OA in patients referred for ankle radiography has no extra value in predicting persistent ankle complaints 2-3 years later if information about BMI, predominant symptoms and chronic complaints is available.



Flowchart of participants included for analyses