Probiotics in Rheumatoid Arthritis and Spondyloarthritis

Subjects: Rheumatology

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The World Health Organization in 2002 defined probiotics as “living organisms in food and dietary supplements that upon ingestion can improve the health of the host beyond their inherent basic nutritional content”. Naturally presents in fruits, raw vegetables, dairy products (in particular fermented ones), they are an integral part of the gut microbiota as a component of commensal flora. The main probiotic microorganisms used in human nutrition are lactic acid bacteria such as Lactobacillus and Bifidobacterium.

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1. Introduction

The World Health Organization in 2002 defined probiotics as “living organisms in food and dietary supplements that upon ingestion can improve the health of the host beyond their inherent basic nutritional content” [1]. Naturally presents in fruits, raw vegetables, dairy products (in particular fermented ones), they are an integral part of the gut microbiota as a component of commensal flora. The main probiotic microorganisms used in human nutrition are lactic acid bacteria such as Lactobacillus and Bifidobacterium [2].

Compared with healthy people, patients with chronic inflammatory diseases, in particular rheumatoid arthritis (RA) and spondyloarthritis (SpA), have an altered gut microbiota called dysbiosis with an increased permeability allowing luminal antigens or bacteria to interact with the host immune system more readily [3][4]. This gut inflammation correlates with systemic inflammation and could be a trigger in developing some autoimmune diseases and participating in their severity [5][6][7][8].

Evidence from mice and human studies revealed that probiotics modulate locally and systemically the immune system, leading to a reduction in mucosal inflammation and pro-inflammatory cytokines [9]. They also alleviate joint inflammation in mice [10]. They can access the intestinal mucosal immune system, persist for a certain amount of time, and initiate a specific immune response. The interaction between probiotic strains and enterocytes is important for the controlled production of cytokines and chemokines secreted by epithelial cells. Indeed, it has been shown that some probiotic organisms can modulate the in vitro expression of pro- and anti-inflammatory molecules in a strain-dependent manner. Indeed, treatment with some Lactobacillus strains reduced gut permeability and decreased arthritic severity [11][12]. The impact of probiotics has already been well studied in atopic diseases and Crohn’s disease, for which they have not shown any real benefit.

Today, the growing interest of patients in the use of complementary therapies is justified by the existence of numerous side effects of usual disease-modifying anti-rheumatic drugs (DMARDS) and symptomatic treatments such as non-steroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids (GCs). Probiotics could represent an alternative and complementary therapy to the standard drugs we already use to control rheumatic activity. However, the effect is not well documented in patients suffering from RA, SpA or psoriatic arthritis (PsA), especially recently, where studies are rare.

The available data from randomized controlled trials are highly heterogeneous in terms of the populations included, the characteristics of the rheumatism, and the results regarding activity scores and inflammatory markers. The three meta-analyses published attempted to provide conclusions on the efficacy of probiotics in patients with inflammatory rheumatism, with disease activity score in 28 joints (DAS28) and C-reactive protein (CRP) as the common primary endpoints. Two focused on RA, and the third included patients with SpA and juvenile idiopathic arthritis (JIA). The number and type of studies included as well as the population studied were therefore not homogeneous, and the results are discordant and difficult to interpret.

2. Discussion

A recent meta-analysis in 2020 reported significant effects in the reduction of blood pressure, lipid profile, BMI and serum glucose [13]. Other evidence has shown their power of reducing intestinal permeability and modulating immune function through direct interaction with the mucosal immune system [14][15]. Immunological studies revealed that probiotics have dose and duration-dependent immunomodulatory effects on B and T cell proliferation and affect pro-inflammatory and anti-inflammatory cytokine regulation [16]. Probiotics administration can restore the normal mucosal barrier function through keeping the balance between intestinal microflora and resistance against harmful bacterial colonization, adherence and translocation [17]. These effects are dependent on the species and strain of bacteria [18]. For instance, oral administration of *Lactobacillus rhamnosus* attenuates various types of experimental arthritis [19]. Increasing evidence suggests that gut dysbiosis in RA and SpA patients favors inflammation, participating in disease activity and severity [20][21]. However, the data on gut microbiota composition are controversial and the strains contained in probiotics are not specifically decreased.

Concerning RA, although a statistically significant decrease in CRP was identified, cautious interpretation is required before inferring clinical significance. First, the reduction in CRP with a MD (95% CI) of −3.04 mg/L (−4.47 to −1.62 mg/L) may not represent a clinically meaningful change. On the other hand, some studies reported normal baseline values of both CRP and ESR, but they did not provide the data and it could not be extracted a posteriori. That may partially explain the absence of significant results regarding DAS28, of which inflammatory markers are one of the components. This systematic review of the literature provided very different baseline characteristics and inclusion criteria for both RA and SpA patients; e.g., only women were included in Alipour et al. [22], the minimum duration of disease progression at inclusion was variable, it had to be either more than 6 months for Zamani's et al., more than 2 years for Vadell et al., one year for the others or unspecified. Despite this, the average disease duration was more than 5 years in all studies, provided longstanding RA and SpA. Therefore, as studies did not provide newly diagnosed RA and SpA, the results cannot be extrapolated to this population. Another limitation of

this meta-analysis is the small sample size, which may affect the reliability and validity of the results. Besides, four studies were monocentric [22][23][24][25], once again limiting the generalization of the results. Those are important limitations to propose the routine use of probiotics in patients with RA.

Concerning DAS28, three studies showed a significant improvement comparing probiotic supplementation with placebo, but results concerning TJC and SJC are not clinically pertinent [22][26][27]. In fact, in Alipour et al., patients in both groups had no or few TJC or SJC. It is important to note that studies included in meta-analyses for evaluation of DAS28, TJC, SJC, CRP, ESR and HAQ are different, which affects the comparability of the results. Furthermore, the control group was different with two studies comparing probiotics with another dietary intervention, no significant effect on DAS-28, CRP, ESR, TJC and SJC was observed in these trials, suggesting a potential confusion bias. Finally, we may suggest that it is not surprising that meta-analysis of Rudbane et al. reports a significant improvement of DAS28 by the fact that the only two studies which reported significant findings were included.

Concerning meta-analyses, as a primary outcome, we analyzed the variation of the values before and after supplementation, as Mohammed et al. and Rudbane et al. did, whereas Lowe et al., who reported significant results, compared final values between each group. This limits their results, as values before intervention were not the same. The strengths of our meta-analysis are that we compared variations in outcome measures (such as DAS28 and CRP) between the two groups and included only studies which were RCTs with low or moderate risk of bias and homogeneous disease populations and added new studies. We were interested in three types of rheumatism because they are the focus of most of the literature data currently available on probiotics and represent the largest proportion of patients with inflammatory rheumatic disease. Concerning DAS28 and CRP, Alipour et al. was excluded from our analysis as the results were not reported in intention to treat. In Vadell et al. and Nenonen et al., an additional dietary intervention was performed which could influence the results, motivating us to exclude them from the meta-analysis. Inclusion of Alipour et al. did not change the results for DAS-28 (SMD (95% CI) of −0.59 (−1.55 to 0.37), p = 0.23; I^2 = 89%; n patients = 189) (data not shown). Furthermore, inulin supplementation (prebiotic) in Zamani et al., 2017 may allow better engraftment of probiotics in the gastrointestinal tract compared to isolated probiotics.

Another strength of our meta-analysis is its methodological quality. We used the “A MeaSurement Tool for Assessing systematic Reviews” (AMSTAR2), designed to carry out rapid and reproducible assessments of the quality of conduct of systematic reviews of RCTs. It represents one of the most widely used instruments to date. Analysis of the methodological quality according to this tool revealed that it was critically low for the three previous meta-analyses. Ours had the advantage of being of higher quality because we removed RCTs at high risk of bias and conducted an adequate investigation of publication bias.

The results of Egger’s test revealed the absence of publication bias for DAS28 (p value = 0.96) and a publication bias for CRP (p value = 0.02). This bias disappeared when sensitivity analyses were performed by removing the studies of Pineda et al. (p value = 0.07) or Mandel et al. (p value = 0.08) (data not shown). Ours to date is the only meta-analysis clearly describing publication bias regarding probiotics supplementation in RA, from which it is

possible to conclude the reliability of the results regarding DAS28. The search for publication bias was theoretically limited by the small number of RCTs available in the literature, but our search strategy was intended to be as complete as possible, including searching for conference abstract data. The number of RCTs included is consistent with previous meta-analyses or higher. This limits the risk of not having included relevant RCTs.

Regarding spondyloarthritis, only two RCTs assessed the efficacy of probiotics supplementation versus placebo on SpA activity. No significant decrease of activity score or well-being was found. It is important to note the disparity between the type of patients included, from peripheral phenotype to ankylosing spondylitis and sacroiliitis confirmed by MRI. It would have been interesting to evaluate the effect of probiotic supplementation in a more homogeneous group of patients because these phenotype differences may have affected the final results. More studies are needed to assess the efficacy of probiotics in this selected population.

Tolerance data are reassuring; however, adverse events were not primary endpoints, therefore this data may have suffered from a lack of collection and precision in its measurement. All studies reported an excellent observance except that of Brophy et al., which suffered from less than 70% of tablets being taken.

Furthermore, it has been shown that drugs influence the intestinal microbiota composition and as such might impact response to probiotics. At baseline, in general, stable antirheumatic medication between one and three months before inclusion were one of the inclusion criteria in RA studies. Almost all patients with RA appeared to be treated with either DMARD or symptomatic treatments such as glucocorticoids or NSAIDs. Only two studies specify the proportion of patients not taking any medication, that of Mandel et al. where it was equal to 6% in the probiotic group (n = 1/15) and 7% in the control group (n = 1/14), and Pineda et al. with 4% in the probiotic group (n = 1/23) and 13.6% in the control group (n = 3/22). However, most of the studies did not mention whether any modification of medication occurred during follow-up, especially biological DMARD (bDMARD), corticosteroids and NSAIDs use, which would be important confounding factors. Disparity in publication years also influence the medications taken by patients, in particular bDMARD. Baseline rheumatism activities were also very different between studies, which influences microbiota composition and possibility of activity variations with intervention.

It is currently difficult to conclude whether probiotics are efficient or not because of a high heterogeneity in studies' design due to the use of different strains, quantities and duration of supplementation. In regard to the heterogeneity present between the RCTs, a large heterogeneity exists between the previous meta-analyses, which can explain the differences in their results concerning the DAS28 and the CRP. Indeed, the main limitation is the wide variety of probiotic strains, administration dose and duration among studies with insufficient power to perform subgroup analysis. No study argued for the dosage of probiotics based on a possible pathophysiological rationale or evidence-based medicine. In addition, strains were not adapted to the profile of the patient's initial microbiota; if they were targeted to a possibly deficient one it would have been interesting to see if the effect was significantly increased, which is currently analyzed with the new generation probiotics.

References

1. Food and Agriculture Organization; World Health Organization. Evaluation of Health and Nutritional Properties of Probiotics in Food including Powder Milk with Live Acid Bacteria; Report of a Joint FAO/WHO Expert Consultation; FAO Food and Nutrition Paper; World Health Organization: Cordoba, Argentina, 2001; Volume 85, pp. 5–35.
2. Wang, P. Probiotic bacteria: A viable adjuvant therapy for relieving symptoms of rheumatoid arthritis. Inflammopharmacology 2016, 24, 189–196.
3. Diamanti, A.P.; Manuela Rosado, M.; Laganà, B.; D'Amelio, R. Microbiota and Chronic Inflammatory Arthritis: An Interwoven Link. J. Transl. Med. 2016, 14, 233.
4. Mielants, H.; De Vos, M.; Cuvelier, C.; Veys, E.M. The Role of Gut Inflammation in the Pathogenesis of Spondyloarthropathies. Acta Clin. Belg. 1996, 51, 340–349.
5. Tlaskalová-Hogenová, H.; Štepánková, R.; Hudcovic, T.; Tucková, L.; Cukrowska, B.; Lodinová-Žádnıková, R.; Kozáková, H.; Rossmann, P.; Bártová, J.; Sokol, D. Commensal Bacteria (Normal Microflora), Mucosal Immunity and Chronic Inflammatory and Autoimmune Diseases. Immunol. Lett. 2004, 93, 97–108.
6. Sartor, R.B. Review Article: Role of the Enteric Microflora in the Pathogenesis of Intestinal Inflammation and Arthritis. Aliment Pharmacol. Ther. 1997, 11 (Suppl. 3), 17–22; discussion 22–23.
7. McCulloch, J.; Lydyard, P.M.; Rook, G.A.W. Rheumatoid arthritis: How well do the theories fit the evidence? Clin. Exp. Immunol. 1993, 92, 1–6.
8. Danning, C.L.; Boumpas, D.T. Commonly Used Disease-Modifying Antirheumatic Drugs in the Treatment of Inflammatory Arthritis: An Update on Mechanisms of Action. Clin. Exp. Rheumatol. 1998, 16, 595–604.
9. Delcenserie, V.; Martel, D.; Lamoureux, M.; Amiot, J.; Boutin, Y.; Roy, D. Immunomodulatory Effects of Probiotics in the Intestinal Tract. Curr. Issues Mol. Biol. 2008, 10, 37–54.
10. Kano, H.; Kaneko, T.; Kaminogawa, S. Oral Intake of Lactobacillus Delbrueckii Subsp. Bulgaricus OLL1073R-1 Prevents Collagen-Induced Arthritis in Mice. J. Food Prot. 2002, 65, 153–160.
11. So, J.-S.; Kwon, H.-K.; Lee, C.-G.; Yi, H.-J.; Park, J.-A.; Lim, S.-Y.; Hwang, K.-C.; Jeon, Y.H.; Im, S.-H. Lactobacillus Casei Suppresses Experimental Arthritis by Down-Regulating T Helper 1 Effector Functions. Mol. Immunol. 2008, 45, 2690–2699.
12. Strowski, M.Z.; Wiedenmann, B. Probiotic Carbohydrates Reduce Intestinal Permeability and Inflammation in Metabolic Diseases. Gut 2009, 58, 1044–1045.
13. Dixon, A.; Robertson, K.; Yung, A.; Que, M.; Randall, H.; Wellalagodage, D.; Cox, T.; Robertson, D.; Chi, C.; Sun, J. Efficacy of Probiotics in Patients of Cardiovascular Disease Risk: A Systematic

Review and Meta-Analysis. Curr. Hypertens. Rep. 2020, 22, 74.

14. Rosenfeldt, V.; Benfeldt, E.; Valerius, N.H.; Paerregaard, A.; Michaelsen, K.F. Effect of Probiotics on Gastrointestinal Symptoms and Small Intestinal Permeability in Children with Atopic Dermatitis. J. Pediatr. 2004, 145, 612–616.
15. Berg, R.D. Bacterial Translocation from the Intestines. Jikken Dobutsu 1985, 34, 1–16.
16. Baharav, E.; Mor, F.; Halpern, M.; Weinberger, A. Lactobacillus GG Bacteria Ameliorate Arthritis in Lewis Rats. J. Nutr. 2004, 134, 1964–1969.
17. Malin, M.; Verronen, P.; Korhonen, H.; Syväoja, E.L.; Salminen, S.; Mykkänen, H.; Arvilommi, H.; Eerola, E.; Isolauri, E. Dietary Therapy with Lactobacillus GG, Bovine Colostrum or Bovine Immune Colostrum in Patients with Juvenile Chronic Arthritis: Evaluation of Effect on Gut Defence Mechanisms. Inflammopharmacology 1997, 5, 219–236.
18. Reid, G.; Jass, J.; Sebulsky, M.T.; McCormick, J.K. Potential Uses of Probiotics in Clinical Practice. Clin. Microbiol. Rev. 2003, 16, 658–672.
19. Nowak, B.; Ciszek-Lenda, M.; Sróttek, M.; Gamian, A.; Kontny, E.; Górska-Frączek, S.; Marcinkiewicz, J. Lactobacillus Rhamnosus Exopolysaccharide Ameliorates Arthritis Induced by the Systemic Injection of Collagen and Lipopolysaccharide in DBA/1 Mice. Arch. Immunol. Ther. Exp. 2012, 60, 211–220.
20. Brusca, S.B.; Abramson, S.B.; Scher, J.U. Microbiome and Mucosal Inflammation as Extra-Articular Triggers for Rheumatoid Arthritis and Autoimmunity. Curr. Opin. Rheumatol. 2014, 26, 101–107.
21. Chen, J.; Wright, K.; Davis, J.M.; Jeraldo, P.; Marietta, E.V.; Murray, J.; Nelson, H.; Matteson, E.L.; Taneja, V. An Expansion of Rare Lineage Intestinal Microbes Characterizes Rheumatoid Arthritis. Genome Med. 2016, 8, 43.
22. Alipour, B.; Homayouni-Rad, A.; Vaghef-Mehrabany, E.; Sharif, S.K.; Vaghef-Mehrabany, L.; Asghari-Jafarabadi, M.; Nakhjavani, M.R.; Mohtadi-Nia, J. Effects of Lactobacillus Casei Supplementation on Disease Activity and Inflammatory Cytokines in Rheumatoid Arthritis Patients: A Randomized Double-Blind Clinical Trial. Int. J. Rheum. Dis. 2014, 17, 519–527.
23. Vadell, A.K.E.; Bärebring, L.; Hulander, E.; Gjertsson, I.; Lindqvist, H.M.; Winkvist, A. Anti-Inflammatory Diet In Rheumatoid Arthritis (ADIRA)—A Randomized, Controlled Crossover Trial Indicating Effects on Disease Activity. Am. J. Clin. Nutr. 2020, 111, 1203–1213.
24. Nenonen, M.T.; Helve, T.A. Uncooked, lactobacilli-rich, vegan food and rheumatoid arthritis. Rheumatology 1998, 37, 274–281.
25. Mandel, D.R.; Eichas, K.; Holmes, J. Bacillus Coagulans: A Viable Adjunct Therapy for Relieving Symptoms of Rheumatoid Arthritis According to a Randomized, Controlled Trial. BMC

Complementary Altern. Med. 2010, 10, 1.

26. Zamani, B.; Golkar, H.R.; Farshbaf, S.; Emadi-Baygi, M.; Tajabadi-Ebrahimi, M.; Jafari, P.; Akhavan, R.; Taghizadeh, M.; Memarzadeh, M.R.; Asemi, Z. Clinical and Metabolic Response to Probiotic Supplementation in Patients with Rheumatoid Arthritis: A Randomized, Double-Blind, Placebo-Controlled Trial. Int. J. Rheum. Dis. 2016, 19, 869–879.
27. Zamani, B.; Farshbaf, S.; Golkar, H.R.; Bahmani, F.; Asemi, Z. Synbiotic Supplementation and the Effects on Clinical and Metabolic Responses in Patients with Rheumatoid Arthritis: A Randomised, Double-Blind, Placebo-Controlled Trial. Br. J. Nutr. 2017, 117, 1095–1102.

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