Anti-inflammatory effect of the specific carbohydrate diet in children with juvenile idiopathic arthritis

Lillemor Berntson (✉ lillemor.berntson@telia.com)

Research article

Keywords: Arthritis, juvenile, anti-inflammatory diet

Posted Date: February 3rd, 2020

DOI: <https://doi.org/10.21203/rs.2.22438/v1>

License: This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

Abstract

Background

Diet has an effect on the intestinal immune system, which may have consequences for inflammatory diseases. Specific carbohydrate diet (SCD) is an effective anti-inflammatory treatment for inflammatory bowel disease in children. We explored the anti-inflammatory effect of SCD in children with juvenile idiopathic arthritis (JIA).

Methods

Twenty-two patients with JIA (age 6.3–17.3 years), with stable, low-to-medium disease activity, were included in the study. Seven children dropped out within two weeks from the start of SCD, and fifteen patients, who completed four to five weeks of SCD, were evaluated in the final analyses. A dietician introduced parents and children to SCD with written and verbal instructions, and regular follow-ups were performed during the intervention period. Patients were studied with clinical and laboratory examinations before, during and after the intervention. In addition to conventional JIA laboratory tests, analyses were performed of short chain fatty acids in faecal samples at inclusion and after two and four weeks of SCD.

Results

SCD significantly decreased morning stiffness ($p = 0.003$) and pain ($p = 0.048$), and improved physical function assessed through the child health assessment questionnaire ($p = 0.022$). Arthritis improved in five of the seven children with arthritis at inclusion. Faecal butyrate increased significantly ($p = 0.020$).

Conclusions

SCD has significant positive effect on arthritis activity, morning stiffness, pain and physical function in children with JIA. Our results suggest that change in bacterial activity of the intestinal canal by dietary intervention may provide an effective and feasible complementary treatment for JIA.

Background

Juvenile idiopathic arthritis (JIA) is an umbrella term which describes a heterogeneous group of rheumatologic diseases that affect children; it is one of the most common chronic paediatric conditions [1]. The diagnosis encompasses seven categories, all sharing the feature of arthritis with a duration of at least six weeks and onset before the age of sixteen years [2].

The cause of the disease is considered to be multifactorial. Both the innate and the adaptive immune system have been shown to be involved in disease pathology [3, 4]. The impact of genetic factors is heterogeneous and not dominant [5]. Environmental risk factors that have been suggested to contribute to the development of JIA include use of antibiotics at early age [6], early weaning from breastfeeding, and delivery by caesarean section [7, 8], all potentially altering the microbiota and intestinal immunity. Increased gut permeability has been shown in several other inflammatory diseases and in one study on JIA [9], suggesting that a dysfunctional gut barrier could increase the possibility for bacteria and other substances to interplay with the immune system, leading to a breakage of T cell tolerance. These factors may affect the likelihood of JIA by influencing the development of the immune system, the integrity of the intestinal mucosal barrier, and the differentiation of immune stimulatory and regulatory cells [10, 11].

As in many other autoimmune diseases, like rheumatoid arthritis (RA), the composition of the bacterial flora seems to be altered in children with JIA, though the results are not consistent [12–15]. In addition to studies on environmental factors and microbiota in JIA, indicating an aberrant microbial setting, there are several studies supporting an important role for gut microbiota in regard to the immune system. The microbiome affects development of the intestinal mucosal barrier [16] and is essential for the normal generation and maturation of gut-associated lymphoid tissue [17, 18]. The microbiome also has an influence on production of TH17 cells.

The occurrence and function of specific phyla, genera or families of bacteria are studied increasingly often and the immunological processes at different levels of the intestinal canal are an important issue. Analyses of the concentration of short chain fatty acids

(SCFAs) in faeces is one way to study function at the colon level. SCFAs, mainly acetate, propionate, and butyrate, are produced by bacteria in the colon through fermentation of insoluble fibres and have been shown to have profound positive immunological effects on the intestinal immune system, in particular in the case of butyrate [19].

One possible way to influence the intestinal canal is through the diet. The specific carbohydrate diet (SCD) has been shown to have beneficial effects in inflammatory bowel disease. The SCD is a nutritionally balanced diet focused on removing many complex carbohydrates such as grains, dairy products except yoghurt fermented for over 24 hours, and vegetables rich in starch and sugars, except monosaccharides like those found in honey. The digestion of these carbohydrates relies on enzymes produced by the microbiota and the large amount of carbohydrates is believed to alter the microbiota. Monosaccharides, on the other hand, can be absorbed by enzymes in enterocytes and are therefore considered to have a smaller impact on the gut microbiota. Furthermore, most processed food is not allowed, as it contains emulsifiers and additives, proven to have a negative impact on the mucus layer in mouse intestines [20]. The diet has been shown to induce clinical and biochemical remission in paediatric Crohn's disease (CD) and ulcerative colitis [21, 22], but not complete healing [23].

The gastrointestinal tract is the largest immune system in the body, yet it is only scarcely studied in JIA. Great advances have been made in treatment of rheumatologic diseases, but even the biological agents do not lead to full response rates in JIA [24, 25]. The aim of this study was to explore if SCD would have an anti-inflammatory effect in children with JIA and thus provide a potential complementary treatment option.

Method

We recruited children and teenagers with JIA, classified according to the International League of Associations for Rheumatology's criteria, at the paediatric rheumatology unit of Uppsala University Children's Hospital in Sweden, from September 2017 to September 2019. Further inclusion criteria were that patients had to be on stable treatment – i.e., there had been no change in medical treatment during the past two to three months, except for joint injections at the latest two months earlier – but not yet in remission, with a mild to moderate disease activity according to Juvenile Arthritis Disease Activity Score (JADAS27) for that category [26]. No child had more than two active joints at inclusion and the erythrocyte sedimentation rate (ESR) was 25 mm at most. Parents and children needed to be motivated to try a dietary intervention as a complementary treatment. Children with any gastrointestinal complaints were investigated and a faecal calprotectin < 100 g/L was required for inclusion. The primary goal was for the child to pursue the diet for four weeks or longer. Before inclusion, the families each received a recipe booklet, a list of allowed products, and a list of recommendations. An initial telephone appointment with a dietician was optional. A visit to the office of the paediatric rheumatology clinic was performed for inclusion.

After the inclusion visit, families were instructed to get familiar with what food to eat and what to avoid during a "learning period" of two weeks at most. After this two-week period, the participants were instructed to follow the SCD diet strictly for at least four weeks, with a follow-up visit after two and four weeks on SCD. At follow-ups, clinical examinations were performed, with weight measured and faecal, urine, and blood samples collected. The child health assessment questionnaire (CHAQ) was filled in [27]. Throughout the trial, the participants had regular contact with and access to the dietician, by email and telephone, and also a physician, by email.

Assessments of CHAQ, JADAS27, morning stiffness in minutes, and pain visual analogue scale (VAS) (0–10 cm) were made at inclusion and after two and four weeks of treatment. Levels of SCFAs in faecal samples from the same occasions were analysed using a high-performance liquid chromatography machine, Agilent technology 1100 series (Agilent Technologies, Inc., Santa Clara, USA). JADAS27 (0–57) is a validated composite disease activity score often used for monitoring patients with JIA [28]. JADAS27 could be used as an inclusion criteria, but not to study results, since it includes the researcher's assessment of disease activity and the results could be biased. It comprises 1) the number of active joints (0–27), 2) patient global assessment VAS (0–10 cm), 3) physician global assessment VAS (0–10 cm), and 4) ESR normalized to a scale 0–10. The endpoints of this study were to examine whether the SCD for four weeks would influence arthritis, clinical pain VAS (0–10 cm), morning stiffness (minutes), physical function assessed through CHAQ, global assessment patient/parent (0–10 cm), and levels of ESR, CRP, and SCFAs in faecal samples.

Statistical analysis

Wilcoxon signed rank test was used as the non-parametric test to estimate significance of differences in clinical and laboratory variables before and during treatment with SCD. The Hodges-Lehmann related sample analysis was used to estimate the confidence interval of the estimated median values. All tests were considered to be significant at $p < 0.05$ and all statistical analyses were performed using IBM SPSS Statistics for Windows, version 25 (IBM Corp., Armonk, NY, USA).

Results

Twenty-two children with different categories of JIA were recruited to this trial and fifteen of them completed the four-week intervention; in some, the follow-up was performed after five weeks. Demographic data are presented in Table 1. Six families dropped out of the study due to lack of motivation; in four, the child turned out not to be motivated enough, and in two, the parents were not motivated. In one family, an acute psychosocial situation stopped participation. Two of the participants did not take part in the two-week visit, because they lived far away from the clinic. Eleven (73%) of the participants were girls and four boys. The median age at inclusion was 13.8 years (IQR: 10.8–16.5) and median disease duration was 3.1 years (IQR: 1.7–7.6). Seven of the fifteen participants had active arthritis at time of inclusion. Faecal calprotectin levels were 0–69 g/l (min–max) at inclusion (reference value 50 g/L). Weight decreased with a median of 2% during the one-month intervention. Five patients were treated with methotrexate before and during the month of intervention, three were on TNF inhibitors (two in combination with methotrexate), two were on abatacept (one in combination with methotrexate), three were treated with NSAIDs, and two received no treatment.

Five of the seven children with arthritis at inclusion did not have any clinical signs of arthritis after four to five weeks of SCD. In two children, one with enthesitis-related arthritis (a category of JIA) and one with juvenile psoriatic arthritis (another category of JIA), the inflammatory activity increased very shortly after inclusion in the study. One of them also developed a virus infection after three weeks on SCD and the JIA was worsened after five weeks on SCD.

Pain VAS and morning stiffness decreased significantly and CHAQ improved significantly during the study period. Patient global assessment VAS improved, but non-significantly (Table 2). The results on pain VAS are shown in Fig 1A, morning stiffness in Fig 1B and CHAQ in Fig 1C. Butyrate in faecal samples increased significantly during the diet, while propionate and total levels of SCFAs increased non-significantly (Fig 1D, Table 3). There was no significant difference in inflammatory blood tests between baseline and week four/five (data not shown), but only four participants had an ESR > 10 at inclusion.

Discussion

Diet is an influencer of the composition and function of the microbiota [29]. Adults with rheumatoid arthritis may be improved by vegan or Mediterranean diet [30–32]. In paediatric CD, feeding with exclusive enteral nutrition (EEN) has been shown to exert a positive influence on intestinal microbiota, and to have an anti-inflammatory and healing effect on the intestinal mucosa, leading to an improved nutritional status and a reduced need for corticosteroids [33]. In Europe, paediatric patients with CD receive EEN during the first six to eight weeks of treatment. Two other diets, SCD and Crohn's disease exclusion diet, have shown positive results in CD [22, 34]. The two diets resemble each other, but are not identical. So far, the only dietary intervention published, conducted on children with JIA, was performed by our group, investigating the anti-inflammatory effect of exclusive enteral nutrition (EEN). The study included only seven children, treated for 3–8 weeks; all of them had an anti-inflammatory effect in clinical and laboratory results, but to varying degrees [35].

In this study, SCD as a complementary treatment in patients with JIA resulted in a significant improvement in morning stiffness, pain, physical function and a significant increase in faecal butyrate concentration, indicating an anti-inflammatory effect from SCD. Participants of this study had a low to median disease activity at inclusion; approximately half of them had morning stiffness and pain as remaining complaints from the disease, in spite of medical treatment. We aimed for a dietary intervention of at least four weeks. Morning stiffness, pain and physical function improved already after two to three weeks in the majority of participants. The inflammatory activity in two patients increased very shortly after inclusion in the study, and the arthritis in those two children did not respond to treatment. In the remaining five with arthritis at inclusion, no clinical sign of arthritis could be found after four/five weeks on SCD. The flare in the two children with no response had already started at inclusion and may be unrelated to SCD, but SCD could not decrease the flare of the disease during the study period.

Laboratory analysis results did not change significantly during the study period, but only four of the children had an ESR > 10 at inclusion. The JADAS27 decreased, but not significantly, and the results could be biased since JADAS27 includes the researcher's subjective assessment of disease activity in the patient.

Our results of a significant increase in butyrate and an increasing, yet non-significant, level of SCFAs in faeces are not surprising, possibly providing confirmation that participants had followed the diet. Fibres and starches found in fruits and vegetables are vital substrates for the production of butyrate and other SCFAs. The SCFAs are proven to have many beneficial functions, such as being an energy substrate for the epithelial cells of the colon. However, they also seem to have more complex functions, such as regulating gene expression and contributing to an anti-inflammatory state of the intestine. Several studies have shown that these microbial metabolites, especially butyrate, have profound effects on T cells, directly and indirectly regulating their differentiation [19, 36]. Low dietary fibres may cause catabolism of the mucous layer, leading to increased permeability and allowing increased contact between luminal bacteria and the epithelium [37]. The composition of the bacterial flora, the diet of the host, and the transit time in the gut are some of the factors influencing the production of SCFAs. While the butyrate level increased in faecal samples from the participants, we do not know if butyrate is involved in regulation of inflammation in children with JIA; most likely, it plays an anti-inflammatory role.

We can only speculate that the elimination of processed food, additives and emulsifiers and restriction of carbohydrates and dairy products play an immunological role in JIA. Processed food often contains exogenous advanced glycation end products (AGEs), these are common in food products that have been heated. Exogenously added AGEs have been shown in animal studies to influence immune and epithelial cells by activating the receptor for advanced glycation end products in various types of cells, such as immune cells, endothelial cells, myocytes, and neurons, but studies in humans have not come that far [38]. The high-fructose corn syrup (HFCS) is a popular sweetener in the food industry, for example in soda. High consumers of sodas have been shown to have an increased risk of arthritis in adults compared with low consumers [39]. HFCS is decreased in SCD compared with in a conventional diet, we lack knowledge about the occurrence of AGEs.

This study on SCD comprised only fifteen patients, and the arthritis was not verified by ultrasound, which are the major weaknesses of the study. Also, children with different categories of the disease on different medical treatments were included, which may have confounded interpretation of results. It would have been preferable to have a control group, which was difficult to arrange in practice.

Making the home-cooked meals required by the SCD was a challenge for many of the families, but the fairly rapid improvement in the majority of the children motivated both parents and children. A strength of the study was that the SCD diet is well-described and studied in children with inflammatory conditions in the digestive tract. Much research remains to understand how diet influences the immune system in children with JIA and how long-lasting the effects are. The results from this study suggest that diet may provide a promising complementary treatment modality for children with JIA.

Conclusions

In this study, four weeks of SCD improved clinical signs and symptoms, and increased faecal butyrate in children with JIA, but not in all cases. Further studies are needed to understand which children, with JIA, may benefit from SCD and how the diet influences the immune system.

Abbreviations

CHAQ: child health assessment questionnaire; CD: Crohn's disease; ESR: erythrocyte sedimentation rate; ILAR: International League of Associations for Rheumatology; JADAS27: Juvenile Arthritis Disease Activity Score 27; JIA: Juvenile idiopathic arthritis; RA: Rheumatoid arthritis; SCFA: short chain fatty acids; SCD: Specific carbohydrate diet; VAS: visual analogue scale.

Declarations

Ethical considerations

The study was approved by the regional ethics committee in Uppsala County (Dnr 2016/263). Oral consent was obtained from all parents and children. Written informed consent was obtained from all parents and from children aged twelve years or older.

Consent for publication

Not applicable

Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available for ethical reasons, as well as privacy reasons, but are available from the author on reasonable request.

Competing interests

The author declares no conflicts of interest

Funding

This work was supported by the Swedish Rheumatism Association [R-657931, R-744331, R-848441], by the Gillbergska foundation, Uppsala, Sweden, and by grants from the Department of Women's and Children's Health, Uppsala University, Uppsala.

Authors' contributions

L.B. has designed, drafted the work, interpreted the data, finalized the manuscript and revised it for publication.

Acknowledgements

The author is grateful to professor Yigael Finkel and medical doctor Niklas Nyström for their support and advice regarding paediatric gastroenterology, to medical student Malin Backlund for her contribution, and to professor Arja Harila-Saari and professor Kjell Alving for commenting on the manuscript. The author is also grateful to professor David Suskind, Seattle, for his positive attitude and supportive words during planning of the study.

Authors' information

L.B. is a consultant in pediatric rheumatology at Uppsala university hospital and associate professor.

References

1. Berntson L, Andersson Gare B, Fasth A, Herlin T, Kristinsson J, Lahdenne P, et al. Incidence of juvenile idiopathic arthritis in the Nordic countries. A population based study with special reference to the validity of the ILAR and EULAR criteria. *J Rheumatol*. 2003;30(10):2275-82.
2. Petty RE, Southwood TR, Manners P, Baum J, Glass DN, Goldenberg J, et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. *J Rheumatol*. 2004;31(2):390-2.
3. Ramanathan K, Glaser A, Lythgoe H, Ong J, Beresford MW, Midgley A, et al. Neutrophil activation signature in juvenile idiopathic arthritis indicates the presence of low-density granulocytes. *Rheumatology (Oxford)*. 2017.
4. van Loosdregt J, van Wijk F, Prakken B, Vastert B. Update on research and clinical translation on specific clinical areas from biology to bedside: Unpacking the mysteries of juvenile idiopathic arthritis pathogenesis. *Best Pract Res Clin Rheumatol*. 2017;31(4):460-75.
5. Hinks A, Cobb J, Marion MC, Prahalad S, Sudman M, Bowes J, et al. Dense genotyping of immune-related disease regions identifies 14 new susceptibility loci for juvenile idiopathic arthritis. *Nat Genet*. 2013;45(6):664-9.
6. Arvonien M, Virta LJ, Pokka T, Kroger L, Vahasalo P. Repeated exposure to antibiotics in infancy: a predisposing factor for juvenile idiopathic arthritis or a sign of this group's greater susceptibility to infections? *J Rheumatol*. 2015;42(3):521-6.

7. Kindgren E, Fredrikson M, Ludvigsson J. Early feeding and risk of Juvenile idiopathic arthritis: a case control study in a prospective birth cohort. *Pediatr Rheumatol Online J*. 2017;15(1):46.
8. Kristensen K, Henriksen L. Cesarean section and disease associated with immune function. *J Allergy Clin Immunol*. 2016;137(2):587-90.
9. Picco P, Gattorno M, Marchese N, Vignola S, Sormani MP, Barabino A, et al. Increased gut permeability in juvenile chronic arthritides. A multivariate analysis of the diagnostic parameters. *Clin Exp Rheumatol*. 2000;18(6):773-8.
10. Arvonen M, Berntson L, Pokka T, Karttunen TJ, Vahasalo P, Stoll ML. Gut microbiota-host interactions and juvenile idiopathic arthritis. *Pediatr Rheumatol Online J*. 2016;14(1):44.
11. Verwoerd A, Ter Haar NM, de Roock S, Vastert SJ, Bogaert D. The human microbiome and juvenile idiopathic arthritis. *Pediatr Rheumatol Online J*. 2016;14(1):55.
12. Di Paola M, Cavalieri D, Albanese D, Sordo M, Pindo M, Donati C, et al. Alteration of Fecal Microbiota Profiles in Juvenile Idiopathic Arthritis. Associations with HLA-B27 Allele and Disease Status. *Front Microbiol*. 2016;7:1703.
13. van Dijkhuizen EHP, Del Chierico F, Malattia C, Russo A, Pires Marafon D, Ter Haar NM, et al. Microbiome analytics of the gut microbiota in juvenile idiopathic arthritis patients: an observational, longitudinal cohort study. *Arthritis Rheumatol*. 2018.
14. Stoll ML, Kumar R, Morrow CD, Lefkowitz EJ, Cui X, Genin A, et al. Altered microbiota associated with abnormal humoral immune responses to commensal organisms in enthesitis-related arthritis. *Arthritis Res Ther*. 2014;16(6):486.
15. Tejesvi MV, Arvonen M, Kangas SM, Keskitalo PL, Pirttila AM, Karttunen TJ, et al. Faecal microbiome in new-onset juvenile idiopathic arthritis. *Eur J Clin Microbiol Infect Dis*. 2015.
16. Kamada N, Seo SU, Chen GY, Nunez G. Role of the gut microbiota in immunity and inflammatory disease. *Nat Rev Immunol*. 2013;13(5):321-35.
17. Bouskra D, Brezillon C, Berard M, Werts C, Varona R, Boneca IG, et al. Lymphoid tissue genesis induced by commensals through NOD1 regulates intestinal homeostasis. *Nature*. 2008;456(7221):507-10.
18. Ivanov II, Honda K. Intestinal commensal microbes as immune modulators. *Cell Host Microbe*. 2012;12(4):496-508.
19. Furusawa Y, Obata Y, Fukuda S, Endo TA, Nakato G, Takahashi D, et al. Commensal microbe-derived butyrate induces the differentiation of colonic regulatory T cells. *Nature*. 2013;504(7480):446-50.
20. Chassaing B, Koren O, Goodrich JK, Poole AC, Srinivasan S, Ley RE, et al. Dietary emulsifiers impact the mouse gut microbiota promoting colitis and metabolic syndrome. *Nature*. 2015;519(7541):92-6.
21. Burgis JC, Nguyen K, Park KT, Cox K. Response to strict and liberalized specific carbohydrate diet in pediatric Crohn's disease. *World J Gastroenterol*. 2016;22(6):2111-7.
22. Suskind DL, Cohen SA, Brittnacher MJ, Wahbeh G, Lee D, Shaffer ML, et al. Clinical and Fecal Microbial Changes With Diet Therapy in Active Inflammatory Bowel Disease. *J Clin Gastroenterol*. 2016.
23. Wahbeh GT, Ward BT, Lee DY, Giefer MJ, Suskind DL. Lack of Mucosal Healing From Modified Specific Carbohydrate Diet in Pediatric Patients With Crohn Disease. *J Pediatr Gastroenterol Nutr*. 2017;65(3):289-92.
24. Shepherd J, Cooper K, Harris P, Picot J, Rose M. The clinical effectiveness and cost-effectiveness of abatacept, adalimumab, etanercept and tocilizumab for treating juvenile idiopathic arthritis: a systematic review and economic evaluation. *Health Technol Assess*. 2016;20(34):1-222.
25. Glerup M, Rypdal V, Arnstad ED, Ekelund M, Peltoniemi S, Aalto K, et al. Long-term outcomes in juvenile idiopathic arthritis: 18 years of follow-up in the population-based Nordic Juvenile Idiopathic Arthritis (JIA) cohort. *Arthritis Care Res (Hoboken)*. 2019.
26. Consolaro A, Giancane G, Schiappapietra B, Davi S, Calandra S, Lanni S, et al. Clinical outcome measures in juvenile idiopathic arthritis. *Pediatr Rheumatol Online J*. 2016;14(1):23.
27. Singh G, Athreya BH, Fries JF, Goldsmith DP. Measurement of health status in children with juvenile rheumatoid arthritis. *Arthritis Rheum*. 1994;37(12):1761-9.
28. Consolaro A, Ruperto N, Pistorio A, Lattanzi B, Solari N, Galasso R, et al. Development and initial validation of composite parent- and child-centered disease assessment indices for juvenile idiopathic arthritis. *Arthritis Care Res (Hoboken)*. 2011;63(9):1262-70.

29. Barratt MJ, Lebrilla C, Shapiro HY, Gordon JI. The Gut Microbiota, Food Science, and Human Nutrition: A Timely Marriage. *Cell Host Microbe*. 2017;22(2):134-41.
30. Hafstrom I, Ringertz B, Spangberg A, von Zweigbergk L, Brannemark S, Nylander I, et al. A vegan diet free of gluten improves the signs and symptoms of rheumatoid arthritis: the effects on arthritis correlate with a reduction in antibodies to food antigens. *Rheumatology (Oxford)*. 2001;40(10):1175-9.
31. Skoldstam L, Hagfors L, Johansson G. An experimental study of a Mediterranean diet intervention for patients with rheumatoid arthritis. *Ann Rheum Dis*. 2003;62(3):208-14.
32. McKellar G, Morrison E, McEntegart A, Hampson R, Tierney A, Mackle G, et al. A pilot study of a Mediterranean-type diet intervention in female patients with rheumatoid arthritis living in areas of social deprivation in Glasgow. *Ann Rheum Dis*. 2007;66(9):1239-43.
33. Zachos M, Tondeur M, Griffiths AM. Enteral nutritional therapy for induction of remission in Crohn's disease. *Cochrane Database Syst Rev*. 2007(1):CD000542.
34. Levine A, Wine E, Assa A, Sigall Boneh R, Shaoul R, Kori M, et al. Crohn's Disease Exclusion Diet Plus Partial Enteral Nutrition Induces Sustained Remission in a Randomized Controlled Trial. *Gastroenterology*. 2019;157(2):440-50 e8.
35. Berntson L, Hedlund-Treutiger I, Alving K. Anti-inflammatory effect of exclusive enteral nutrition in patients with juvenile idiopathic arthritis. *Clin Exp Rheumatol*. 2016.
36. Koh A, De Vadder F, Kovatcheva-Datchary P, Backhed F. From Dietary Fiber to Host Physiology: Short-Chain Fatty Acids as Key Bacterial Metabolites. *Cell*. 2016;165(6):1332-45.
37. Desai MS, Seekatz AM, Koropatkin NM, Kamada N, Hickey CA, Wolter M, et al. A Dietary Fiber-Deprived Gut Microbiota Degrades the Colonic Mucus Barrier and Enhances Pathogen Susceptibility. *Cell*. 2016;167(5):1339-53 e21.
38. Snelson M, Coughlan MT. Dietary Advanced Glycation End Products: Digestion, Metabolism and Modulation of Gut Microbial Ecology. *Nutrients*. 2019;11(2).
39. DeChristopher LR, Uribarri J, Tucker KL. Intake of high-fructose corn syrup sweetened soft drinks, fruit drinks and apple juice is associated with prevalent arthritis in US adults, aged 20-30 years. *Nutr Diabetes*. 2016;6:e199.

Tables

Table 1. Clinical characteristics of fifteen children with juvenile idiopathic arthritis, treated with specific carbohydrate diet for four weeks.

Patient ID	Gender	ILAR category ^a	Age at onset, years	Age at inclusion, years	Clinical features at inclusion	Treatment during study	ANA ^b	HLA-B27 ^d
1	F	Oligo pers	16.0	17.3	Arthritis, one big joint	None	Neg	Pos
2	F	ERA	14.0	14.3	Arthralgia + morning stiffness	NSAID	Neg	Pos
3	M	Oligo pers	2.9	9.0	Arthritis, one big joint	None	Pos	na ^c
4	F	Juv psoriatic	13.6	16.7	Morning stiffness	NSAID	Neg	na ^c
5	F	Poly RF ⁻	13.6	16.5	Morning stiffness	Methotrexate	Neg	Neg
6	F	Oligo ext	3.0	13.8	Arthritis, one big joint + uveitis	Infliximab	Neg	na ^c
7	F	Oligo pers	3.2	11.7	Pain + stiffness after physical activity, post uveitis	Abatacept + Methotrexate	Neg	na ^c
8	F	Poly RF ⁻	8.0	10.8	Arthritis, one big joint	Abatacept	Pos	na ^c
9	M	Poly RF ⁻	13.7	17.1	Arthritis, one big + one small joint	Methotrexate	Pos	Neg
10	F	Oligo pers	10.8	14.4	Inflammatory back pain	Etanercept + Methotrexate	Neg	Neg
11	F	Oligo pers	5.6	9.5	Morning stiffness, recurrent joint injections	Methotrexate	Pos	na ^c
12	F	Oligo pers	3.7	11.2	Joint pain after physical activity, post uveitis	Infliximab Methotrexate	Pos	na ^c
13	M	Oligo pers	1.5	14.6	Arthritis, one big joint	Methotrexate	Neg	Neg
14	F	Oligo pers	5.6	6.3	Morning stiffness, pain	Methotrexate	Neg	na ^c
15	M	ERA	9.4	10.9	Arthritis, one big joint	None	na ^c	Pos

^aILAR, International League of Associations for Rheumatology; oligo pers, oligoarticular persistent; ERA, enthesitis-related arthritis; juv psoriatic, juvenile psoriatic; poly RF⁻, polyarticular rheumatoid factor negative; oligo ext, oligoarticular extended.

^bANA, antinuclear antibodies.

^cna, not analysed.

^dthe human leukocyte antigen B27.

Table 2. Estimates before, compared to at four weeks of SCD treatment in fifteen children with juvenile idiopathic arthritis.					
Variable Md (IQR)	At inclusion	At 4 weeks of SCD	Median difference	Confidence interval ^a	p-value ^b
Pain VAS (mm) ^c	28 (21-40)	23 (2-38)	-13.2	(-22.5) - (-2.0)	0.048
Morning stiffness (min)	30 (0-60)	0 (0-10)	-27.5	(-40.0) - (-10.0)	0.003
CHAQ (0-3) ^d	0.38 (0.25-1.0)	0.25 (0-0.5)	-0.25	(-0.44) - (-0.06)	0.022
Patient Global Assessment VAS Score (mm)	2.3 (1.2-5.7)	2.0 (0.2-4.7)	-1.4	(-1.8) - (-0.7)	0.069
JADAS27	4.1 (3.4-8.2)	3.9 (0.4-9.8)	-2.0	(-0.38) - (0.5)	0.065

^aHodges-Lehmann related sample analysis

^bWilcoxon matched-pair signed rank analysis

^cPain VAS= Pain Visual Analogue Scale

^dCHAQ= Child Health Assessment Questionnaire

Table 3. Levels of short chain fatty acids in fecal samples before, compared to at four weeks of SCD treatment in fifteen patients with juvenile idiopathic arthritis

SCFA mg/g	At inclusion Md (IQR)	At 4 weeks of SCD	Median difference	Confidence interval ^a	p-value ^b
Butyrate	0.75 (0.44-1.32)	1.15 (0.87-1.99)	0.51	0.08-1.04	0.02
Propionate	0.87 (0.50-1.01)	0.94 (0.59-1.30)	0.16	(-0.01) - (0.38)	0.06
Acetate	3.05 (2.22-3.74)	3.70 (2.12-5.34)	0.45	(-0.51) - (1.07)	0.33
Valerate	0.10 (0.04-0.15)	0.11 (0.06-0.17)	0.02	(-0.05) - (0.10)	0.46
Total	5.36 (3.61-6.77)	6.59 (4.23-8.54)	1.14	(-0.19) - (2.42)	0.07
^a Hodges-Lehmann related sample analysis					
^b Wilcoxon matched-pair signed rank analysis					

Figures

Fig. 1

Figure 1

A–D. Levels of pain on visual analogue scale (0–100 mm) (1A); Morning stiffness (minutes) (1B); Child health assessment questionnaire, CHAQ (0–3) (1C); Concentration of butyrate (mg/g) in faecal samples (1D). All at inclusion and after two and four weeks of specific carbohydrate diet. *Wilcoxon matched-pair signed rank analysis comparing levels at inclusion with levels after four weeks of specific carbohydrate diet.