EJR European Journal of Rheumatology

DOI: 10.5152/eurjrheum.2017.16103

Literature Review

Relationship between diet and ankylosing spondylitis: A systematic review

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Abstract

The question of whether diet plays a role in the onset of ankylosing spondylitis (AS) or can affect the course of the disease is an important one for many patients and healthcare providers. The aims of this study were to investigate whether: 1) patients with AS report different diets to those without AS; 2) amongst patients with AS, diet is related to severity; 3) persons with particular diets are less likely to develop AS; 4) specific dietary interventions improve the AS symptoms. The review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Medline, Embase, Cochrane Library, and reference lists of relevant articles were searched. Two authors independently selected eligible studies, assessed the quality of included trials, and extracted the data. Sixteen studies (nine observational and seven interventions) were included in the review. Due to the heterogeneity of the study designs and analyses, the results could not be aggregated. Evidence on a possible relationship between AS and diet is extremely limited and inconclusive due to the majority of included studies being small, single studies with moderate-to-high risk of bias, and insufficient reporting of results.

Keywords: Ankylosing spondylitis, rheumatic disease, diet, nutrition, systematic review

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Cite this article as: Macfarlane TV, Abbood HM, Pathan E, Gordon K, Hinz J, Macfarlane GJ. Relationship between diet and ankylosing spondylitis: a systematic review. Eur J Rheumatol 2018; 5: 45-52.

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Submitted: 25 November 2016
Accepted: 12 April 2017
Available Online Date: 25 October 2017

Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory rheumatic disease with estimated prevalence per 10,000 of 23.8 in Europe, 16.7 in Asia, 31.9 in North America, 10.2 in Latin America, and 7.4 in Africa (1). AS adversely affects patients in terms of symptoms such as pain and fatigue, leading to impaired function and diminished quality of life (2, 3). Despite the development of biological therapy, which has revolutionized the treatment of AS, many patients explore complementary treatments such as dietary therapy (4).

There is overwhelming evidence of the importance of diet in the etiology of a wide range of diseases such as rheumatoid arthritis (RA), cardiovascular disease, and cancer (5-7). An examination of dietary patterns in a large cohort of nurses in the United States found that dietary patterns characterized by high intakes of fruit, vegetables, legumes, whole grains, poultry, and fish, were associated with a reduced risk of RA. In contrast, dietary patterns typical of industrialized countries (high intake of red meats, processed meats, refined grains, French fries, desserts and sweets, and high-fat dairy products) were associated with an increased risk of RA (8). A meta-analysis of placebo-controlled trials in patients with RA reported that that dietary fish oil has a modest effect in reducing tender joint count and morning stiffness, an effect attributed to the anti-inflammatory mechanism of omega-3 polyunsaturated fatty acids (9).

It has been suggested that a low starch diet leads to lower AS disease activity and that *Klebsiella pneumoniae,* which can be influenced by starch consumption, is a triggering factor involved in the initiation and development of AS (10-13).

Although some publications have considered the evidence linking AS with diet, there have been no systematic evaluations of the evidence (14-19).

The objectives of this systematic review were to investigate whether:

1) patients with AS report different diets to those without AS;
2) amongst patients with AS, diet is related to severity;
3) persons with particular diets are less likely to develop AS;
4) specific dietary interventions improve the symptoms of AS.

Methods

The review protocol was registered with PROSPERO, an international register of systematic reviews (registration number: CRD42015026699) (20). We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (21).

Literature search strategy

The search terms relating to AS (AS, spondyloarthropathy, spondylitis, and spondyloarthritis) were combined with terms relating to diet (diet, nutrition, food, food habits, nutritional status, vitamins, antioxidants, fatty acids, carbohydrates, dietary protein, calcium, fish oils, fruit, vegetables, and micronutrients) to find articles published in Embase and Medline up to August 2016. Additionally, two journals (Annals of the Rheumatic Diseases and Annual Review of Nutrition) were searched manually from 2010 to 2015. The references of the retrieved manuscripts were screened for further relevant papers.

Inclusion and exclusion criteria

We included all observational studies on humans (cross-sectional, cohort, case-control, and case series studies), but we excluded case reports. We also excluded case series with a small number of study participants (<5). Uncontrolled treatment outcome studies and randomized controlled trials (RCT) were also included. Participants had to be at least 18 years old. We considered studies published in English that evaluated the presence of AS (or axial spondyloarthritis (axSpA)) using established criteria or clinical diagnosis, included diet assessment, and quantified an association between AS (or axSpA) and diet. In this review, we did not consider alcohol consumption.

Data extraction

Two independent reviewers screened the title and the abstract of each study following the inclusion criteria. If disagreement occurred between the two reviewers, a third reviewer was consulted.

For eligible studies, data extraction was performed by two independent reviewers using a specially designed data collection form.

Assessment of study quality

We used the Scottish Intercollegiate Guidelines Network (SIGN) methodology checklists to assess the quality of individual studies (22). Two reviewers independently conducted the quality assessment. If a disagreement occurred, a third reviewer was consulted.

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach was used to rate the quality of evidence (23, 24).

Results

Search results

The search of the databases yielded 582 publications (Figure 1). After the removal of irrelevant papers (n=512) and duplicates (n=18) and having found 10 additional papers from other sources including searching the references of full-text papers, 58 full-text published papers, 2 letters, and 5 conference abstracts were considered. After further consideration, 3 abstracts were removed because they did not include the necessary information and 46 full-text articles were removed because they did not report AS (n=3), did not look at relationship between AS and diet (n=2), included children (n=1), had a very small sample of AS patients (n=4), contained case reports (n=3), did not report information on diet (n=1), was in the Chinese language (n=1), did not report diet (n=25), did not report information on AS (n=2), and were non-systematic reviews (n=3) and thesis (duplicate publication, n=1). There were a total of 16 studies included in the review, 10 of which were full-text papers, two were letters, two studies were summarized in review articles, and two were conference abstracts (25-40).

Description of the included studies and participants

Multiple studies were conducted in Sweden and United Kingdom, and individual studies in Norway, Belgium, France, Australia, New Zealand, China, Portugal, and Turkey (Table 1, Appendix 1) and were published between 1991 and 2014 (25-35, 37-40). Eight of the included studies were case series; four were treatment outcome studies with all the participants receiving intervention, three were randomized clinical trials, one was a case-control study, and one study investigated the gene-environment interaction using a case-only design (25-35, 37-40). All of the studies were conducted in a hospital setting, except one study that recruited participants *via* a Web site (Table 1, Appendix 1) (28). Eight studies only reported inclusion criteria, while three others only reported exclusion criteria.

Participation rate was reported by three studies describing a case series (range: 46%–93%) and one case-control study (25, 29, 32, 34) (89%). None of the treatment outcome studies reported a follow-up rate, while the follow-up rate in RCTs was between 65% and 100% (28, 30). The minimum duration of the follow-up was 3 months and the maximum, 10 months (Table 1, Appendix 1).

The study size ranged from 12 to 293 participants (26, 39). Among the 11 studies that reported gender distribution, females comprised between 19% and 38% (27, 31). Among the 10 studies that reported age distribution, the mean age ranged between 30 and 50 years (31, 32). Only 8 studies specified the disease duration with the mean ranging between 9 and 27 years (Table 1, Appendix 2) (30, 32).

Among the nine studies that reported the diagnostic criteria for AS, the most common was the modified New York criteria reported by five studies, the European Spondyloarthropathy Study Group (ESSG) reported by four studies, the Amor criteria by two studies, and the Assessment of Spondyloarthritis International Society (ASAS) classification criteria by one study (Table 1, Appendix 2) (26, 29-35, 40-44).

The following criteria were used to measure disease activity: the Bath Ankylosing Disease Activity Index (BASDAI) (9 studies), Bath Ankylosing Functional Index (BASFI) (7 studies), Bath AS Patient Global Score (BASG) (3 studies), AS Quality of Life (ASQoL) index (2 studies), ASAS, and ASAS20 (one study), SF-36 (2 studies), erythrocyte sedimentation rate (ESR) (5 studies), C-reactive protein (CRP) (5 studies), aggravation of symptoms, change from baseline, visual analog scale (VAS), and medication requirement (Table 1, Appendix 2) (25, 27, 30, 32, 35, 36, 45-51).

Availability of information on diet and nutrition

In the observational studies, the assessment of diet was conducted using a questionnaire with three studies using a validated, 84-question, semi-quantitative, food-frequency questionnaire (FFQ). Other methods used were maintaining a food diary, face-to-face interview, interview with a dietician, and telephone survey (Table 1, Appendix 2) (25, 26, 29, 31-34, 39, 40, 52, 53).

Studies examined different types of food and nutrients in relation to AS, most commonly regarding the consumption of starch, dairy, and different types of diet (Table 2, 3, Appendix 3).

Quality of studies

As studies included in this systematic review had different designs, their quality was assessed separately as case series (Appendix 4), treatment outcome studies (Appendix 5), case-control study (Appendix 6), and RCTs (Appendix 7).

The quality could not be fully assessed in studies published as abstracts, letters, or described in reviews (35-40). Overall, the GRADE quality of evidence was low or very low with only two

Table 1. Description of studies

Description	N or (min, max) as appropriate
Total	16
Publication year	1991, 2014
Country	
Norway	1
Belgium	1
United Kingdom	3
France	1
Sweden	4
Australia	1
New Zealand	1
China	1
Portugal	1
Turkey	1
Italy	1
Study type	
Observational	9
Case-control	1
Case series	8
Intervention	7
Uncontrolled treatment outcome	4
Randomized clinical trial (RCT)	3
Study size	12. 439
Gender	
% females	19. 56
Not reported	4
Age (years)	30,50
Not reported	5
AS diagnostic criteria	
Modified New York	5
European Spondyloarthropathy Study Group (ESSG)	4
Amor	2
Assessment of Spondyloarthritis International Society (ASAS)	1
Hospital diagnosis (not specified)	7
Measure of disease activity	
Bath Ankylosing Disease Activity Index (BASDAI)	9
Bath Ankylosing Functional Index (BASFI)	7
Bath AS Patient Global Score (BASG)	3
AS Quality of Life (ASQoL)	2
Assessment of Spondyloarthritis International Society (ASAS)	1
36-Item Short Form Health Survey (SF-36)	2
Erythrocyte sedimentation rate (ESR)	5
C-reactive protein (CRP)	5
Medication requirement	2
Aggravation of symptoms	1
Change from baseline	1
Visual analog scale (VAS)	1
Assessment of diet	
Questionnaire	5
Interview	2
Telephone interview	1
Food diary	1
Intervention	7

AS: ankylosing spondylitis

studies, both of them RCTs, fully satisfying the quality criteria (Table 2, 3) (28, 30). In studies of intervention, compliance was assessed by questioning the participants about adherence to the diet, by counting the remaining capsules, by asking the participants to report on the number of study capsules that they had taken during the previous week, or by asking the participants to return all the study drug containers for weighing (27, 28, 30, 35, 37).

Most studies, especially more recent, used modern statistical methods and investigated the effects of potential confounding factors such as age, gender, smoking, and body mass index (BMI) (Appendix 8).

None of the studies investigated data to answer whether persons with particular diets are less likely to develop AS (Objective 3).

Objective 1: Comparison of diet in patients with AS and those without AS

Only one case-control study investigated whether diet differs among AS patients as compared to persons without AS (Table 2, 3) (34). The calculated energy intake was significantly higher among AS patients as compared to the controls (1,940 vs. 1,819 kcal, $p<0.05$). The difference in the calculated energy intake persisted even after adjusting for physical activity level, weight, sex, and age. Apart from differences that were not significant, i.e., a lower intake of monounsaturated fats ($p=0.07$) and total fat ($p=0.07$) among the patients, there were no other differences in diet (consumption of dairy products, fish, meat, fruits, and vegetables) when compared with the controls (Appendix 10-13).

Ge et al. (31) performed an association study examining the gene–environment interaction between IL-1F7 gene polymorphisms and measures of dietary exposure. There was an interaction with the type of cooking oil with an increased risk for cooking using half plant–half animal fats (OR 4.27, 95% CI 1.59-11.48, $p=0.004$). The interaction between IL-1F7 alleles and other factors such as salt, meat, or vegetable consumption in AS patients was not statistically significant (all $p>0.05$) (Table 2, 3; Appendix 12-14).

Objective 2: Diet and severity of AS (observational studies)

Overall, the evidence interlinking diet and AS severity was limited, and we were unable to perform a meta-analysis due to the lack of reports with data, diversity in outcome, and definition of exposure.

Haugen et al. (25) reported that 78% of AS patients believed that diet influenced the

Table 2. Summary of findings (types of food/diet)

Exposure	Outcome								
Food/diet	Patients with AS vs. controls			Dietary consumption and severity of AS			Dietary intervention and severity of AS		
	Participants (studies)	Result	Quality of evidence (GRADE)	Participants (studies)	Result	Quality of evidence (GRADE)	Participants (studies), follow-up	Result	Quality of evidence (GRADE)
High starch food	-	-	-	405 (2) 12 (1) 12 (1) 111 (1)	- BASDAI: No association (no data) - ESR, CRP, SF-36: No association - BASDAI, BASFI, BASG: Sign. association - Symptom aggravation	Very low	110 (2), 9-10 months 36 (1), 9 months	Low starch diet: Sign. reduction in ESR Symptom improvement (no data)	Very low
Dairy products	77 AS/307 controls (1)	No sign. difference	Low	504 (3)	BASDAI: No association (no data)	Very low	25 (1), 9 months	Dairy excl. diet: Self-reported therapeutic effect	Very low
Fish/fish oil	77 AS/307 controls (1)	Fish consumption: No sign. difference	Low	111 (1)	Fish consumption: No association (no data)	Very low	18 (1), 21 weeks	High- vs. low-dose fish oil: No sign. difference	Very low
Meat and meat products	77 AS/307 controls (1) 150 AS only (1)	- No sign. difference - Non-sign. gene IL-1F7 interaction	Low	404 (2)	BASDAI: No association (no data)	Very low	-	-	-
Fruit and vegetables	77 AS/307 controls (1) 150 AS only (1)	- No sign. difference - Non-sign. gene IL-1F7 interaction	Low	111 (1)	Symptom aggravation	Very low	-	-	-
Probiotic supplements	-	-	-	-	-	-	18 (1), 4 weeks 196 (2), 12 weeks	- BASDAI, VAS: Sign. association - BASFI, ESR, CRP: No association BASDAI, VAS, BASFI, CRP, ASQoL: No sign. difference compared to placebo	Low
CAM	-	-	-	75 (1)	BASDAI, BASFI, BASG, ASQoL, ESR, CRP: No association	Very low	-	-	-
Cooking oil	150 AS only (1)	Sign. gene IL-1F7 interaction (half plant–half animal fat)	Low	-	-	-	-	-	-
Salt consumption	150 AS only (1)	Non-sign. gene IL-1F7 interaction	Low	100 (1)	BASDAI: No association (no data)	Very low	-	-	-
Convenience food	-	-	-	293 (1) 100 (1)	BASDAI: No association with consumption of canned or frozen food (no data); Sign. inverse association with number of meals taken out of home BASDAI: No association with fast food consumption (no data)	Very low	-	-	-

AS: ankylosing spondylitis; BASDAI: Bath Ankylosing Disease Activity Index; ASQoL: AS Quality of Life; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; SF-36: 36-Item Short Form Health Survey; BASDAI: Bath Ankylosing Disease Activity Index; BASFI: Bath Ankylosing Functional Index; BASG: Bath AS Patient Global Score; VAS: visual analog scale; GRADE: Grading of Recommendations Assessment, Development, and Evaluation system

Table 3. Summary of findings (nutrients)

Exposure	Outcome					
	Patients with AS vs. controls			Dietary consumption and severity of AS		
Nutrient	Participants (studies)	Result	Quality of evidence (GRADE)	Participants (studies)	Result	Quality of evidence (GRADE)
Energy	77 AS/307 controls (1)	Sign. higher in cases	Low	111 (1)	BASDAI: No association (no data)	Very low
Protein	77 AS/307 controls (1)	No sign. difference	Low	177 (2)	BASDAI, ESR, CRP: No association	Very low
Carbohydrate	77 AS/307 controls (1)	No sign. difference	Low	177 (2)	BASDAI, ESR, CRP: No association	Very low
Fat	77 AS/307 controls (1)	No sign. difference	Low	111 (1) 66 (1)	BASDAI: Sign association in females only BASDAI, ESR, CRP: No association	Very low
Fiber	77 AS/307 controls (1)	No sign. difference	Low	111 (1)	BASDAI: No association (no data)	Very low
Saturated fatty acids	77 AS/307 controls (1)	No sign. difference	Low	177 (2)	BASDAI, ESR, CRP: No association	Very low
Mono-unsaturated fatty acids	77 AS/307 controls (1)	No sign. difference	Low	-	-	-
Poly-unsaturated fatty acids	77 AS/307 controls (1)	No sign. difference	Low	177 (2) 66 (1)	BASDAI, CRP: No association ESR: Sign. association	Very low
Linoleic acid	77 AS/307 controls (1)	No sign. difference	Low	66 (1)	BASDAI, ESR, CRP: No association	Very low
Alpha-linoleic acid	77 AS/307 controls (1)	No sign. difference	Low	66 (1)	BASDAI, ESR, CRP: No association	Very low
Long-chain omega-3 fatty acids	77 AS/307 Controls (1)	No sign. difference	Low	177 (2) 66 (1)	BASDAI, CRP: No association ESR: Sign. association	Very low

AS: ankylosing spondylitis; BASDAI: Bath Ankylosing Disease Activity Index; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; GRADE: Grading of Recommendations Assessment, Development, and Evaluation system

symptoms of their disease and one-third of the patients reported worsening symptoms after the intake of certain foods with 35% mentioning increased swelling of the joints. Foods most frequently implicated were meat, coffee, sweets, sugar, chocolate, citrus fruits, and apples. Sixteen percent of the AS patients had been through a fasting period on their own initiative with a majority of them reporting less pain, less stiffness, and less joint swelling. Twenty-two percent of patients with AS in an attempt to alleviate disease symptoms had previously tried diets such as lactovegetarian or vegan diets (Appendix 16).

Of the four studies reporting data on the relationship between foods high in starch and AS severity, two were conference abstracts (Appendix 9, Table 2) (26, 32, 39, 40). While one study reported a significant association of daily starch intake with BASDAI, BASFI, and BASG, other studies did not find an association between the consumption of foods high in starch and BASDAI (26, 39, 40). There was no association of daily starch intake with SF-36, CRP, or ESR (39). A small proportion of patients (1.8%) reported aggravation of symptoms associated with food rich in flour (32). Silva (39) reported that the average starch intake was significantly, positively associated with BASDAI, BASFI, and BASG, but not with SF-36, CRP, or ESR. The linear regression showed increases of 3%, 3.9%, and 2.9% in BASDAI, BASFI, and BASG scores, respectively, by milligram of ingested starch. The authors concluded that the higher intake of starch was related to increased disease activity and greater functional impairment.

Three studies that reported data on the relationship between the consumption of dairy products and AS did not find any association with BASDAI (Table 2, Appendix 10) (26, 32, 40). One study that reported a case series did not find an association between the consumption of fish and dietary omega-3 fatty acid and BASDAI (Table 2, Appendix 11) (32).

Sundström et al. (32) reported in a study of 111 patients that 7 patients experienced aggravated arthralgia or AS symptoms associated with a particular foodstuff, most commonly vegetables or fruits (n=2) or food rich in flour (n=2) (Appendix 9, 12, Table 2).

Taşpınar et al. (40) reported no association between the consumption of salt and fast food and the BASDAI. Claudepierre et al. (26) reported that among the dietary factors, the frequency of meals taken out of home was the only variable related (negatively) to disease activity. The mean (SD) BASDAI score among those eating out of home twice per week or less was 5.1 (2.1) as compared to 4.1 (2.1) among those who ate out of home more than twice per week ($p<0.001$) (Table 2, Appendix 14).

Sundström et al. (33) reported that there was no correlation between dietary fat intake and disease activity assessed by BASDAI. ESR correlated negatively with the dietary total polyunsaturated fatty acids (PUFA) and omega-3 long-chain polyunsaturated fatty acids (LCPUFA) ($rs=-0.25$ and $rs=-0.27$, respectively, $p<0.05$). While no overall correlation between dietary intake and disease activity was found, as measured by BASDAI, there were negative correlations between the percentage energy intake derived from fat and saturated fats with BASDAI ($rs=-0.43$, $p<0.05$ and $rs=-0.50$, $p<0.01$, respectively) (32) (Appendix 8, Table 3).

Sundström et al. (32) stated that 32 patients (29%) reported that they had consumed herbal products, multivitamins, and other food supplements during the preceding 2 weeks. The most common were omega-3 (n=13; median intake: 1 g/day), multivitamin and/or multimineral (n=12), and iron (n=4) supplements. (Table 2, Appendix 15).

Chatfield et al. (29) reported that 82.7% AS patients used complementary and alternative medicine (CAM) and out of these patients, 16

(25.8%) were using 7 or more types. Forty-four AS patients (72.1%) reported a form of dietary CAM among whom 28 (37.4%) were using multiple types at the time of study. The most common dietary CAMs were fish oil (26.7% of the study population), green tea (25.3%), vitamin supplements (24.0%), and glucosamine (21.3%). Out of a total of 89 dietary CAMs, only 10 were initiated by a CAM practitioner and 50 were reported to be of little or no benefit. There was no significant difference between the dietary CAM users and non-users across a range of disease indices (ESR, CRP, BASDAI, BASFI, ASQoL, or BASG) (Table 2, Appendix 15).

Objective 4: Dietary interventions and AS symptoms

Appelboom et al. (35) investigated, in a single-arm intervention study of 25 patients, whether a diet that excluded dairy products, was beneficial for the course of the disease or not. The results after six weeks of follow-up showed relatively good compliance to the diet (72%). Amongst the participants, 52% reported good improvement out of which 62% could discontinue their nonsteroidal anti-inflammatory drugs (NSAID) therapy. When follow-up of the responders was carried out for 80% out of the 15 patients at 3 months, all the 10 patients at 6 months, and 89% out of 9 patients at 9 months, it was found that they were satisfied and had continued the dietary regime. The authors reported that six patients were still observing the diet after two years of follow-up and remained free from any other therapy (Table 2, Appendix 10).

Ebringer and Wilson (37) in a single-arm intervention study of a low starch diet in 36 AS patients, reported a significant reduction ($p<0.001$) in ESR levels over a 9-month period. Further, a majority of the participants reported that the severity of symptoms declined, and in some cases, disappeared. Some patients noticed a decrease in the requirement for NSAIDs; however, no precise figures were reported. The authors reported that they treated over 450 AS patients from 1983 onwards and that over half of these patients did not require any medication at follow-up. Ebringer et al. (38) reported a decrease in ESR in a single-arm intervention study of low starch, high protein, high vegetable, and fruit diet with 10 months follow-up; however, precise figures were not reported (Table 2, Appendix 9).

Sundström et al. (27) reported a randomized trial of high- versus low-dose fish oil with 21 weeks of follow-up with participants blinded to the dose. At the end of the study, there was a statistically significant decrease in the BASDAI scores ($p=0.038$) in the high-dose group and a statistically significant increase in the ESR in the low-dose group ($p=0.027$), but no other significant differences. However, a statistically significant difference was not found when comparing the high- and low-dose groups (Table 2, Appendix 11).

A small uncontrolled intervention study investigated the effects of giving *Lactobacillus acidophilus* and *Lactobacillus salivarius* daily for 4 weeks to 18 patients with quiescent ulcerative colitis but active SpA (36). Significant improvements were seen in BASDAI (reduction in mean (SD) from 5.8 (1.5) at the baseline to 4 (1.8) at follow-up, $p<0.05$) and pain VAS (reduction from 58.1 (16.8) to 41.5 (14.3), $p<0.05$). However, neither of the two RCTs found a significant effect of probiotic supplementation on the AS outcome such as disease activity, function, well-being, BASDAI, BASFI, pain levels, CRP, or ASQoL (28, 30).

We did not perform a meta-analysis due to the diversity of outcomes and types of probiotic supplements (Table 2, Appendix 15).

Discussion

This is the first systematic review to examine the association between AS and diet. It has shown that only a few, relatively small, and mainly observational studies have been conducted in this field. From the 16 articles included in the review, there is little evidence regarding the fact that aspects of diet influence the severity of AS or are part of its etiology. In particular, there is no evidence that a reduction in starch intake, exclusion of dairy products, consumption of fish and fish oil or probiotic supplementation reduce susceptibility toward AS or diminish AS symptoms.

This review has many methodological limitations. Firstly, there is scarce literature on the topic and 6 out of 16 studies were not published as full reports and, therefore, limited data were available for data extraction. Several studies did not report the actual figures and analysis results. The studies included in this review vary extensively in design, AS diagnostic criteria, measures of disease severity, exposure measured, measurement instruments, intervention, and duration of follow-up. Therefore, it was not possible to conduct a meta-analysis.

Although we limited our search to publications in the English language, the studies included in this review were from 10 countries. Most studies were conducted in a hospital setting, except one study that used a patient society Web site (28). The participation rate and the participants' selection method were not stated in the majority of the studies and, therefore, it was difficult to determine how representative they were, limiting the generalizability of the findings. Most studies, especially more recent, used appropriate statistical methods and investigated the effects of potential confounding factors.

Retrospective assessment of dietary exposure may introduce recall bias. However, observational studies included in this review seem to evaluate the current dietary habits, except one study that collected information on special diets and food avoidance in the past three months and one study that used a food diary over five consecutive days (29, 39). In addition, when assessing dietary risk factors in prevalent cases of AS, it is difficult to ascertain if the diet influences the development of AS over the course of the disease. It is also common for people to change their diets soon after the onset of disease and, therefore, the current diet may not actually represent past dietary intake. A validated FFQ was used in three observational studies from the same research group, and reproducibility was assessed in the study by Haugen et al. (25); however, the reliability and validity of the dietary data collected in the other studies was not clear (32, 34).

The majority of AS patients (78%) as well patients with other rheumatic diseases (RA, 64%; juvenile rheumatoid arthritis (JRA), 88%; psoriatic arthropathy, 71%; osteoarthrosis, 65%) believe that diet influences their disease symptoms (25). This suggests that if diet is important, it may influence the inflammatory process across rheumatic diseases.

Studies involving AS and other rheumatic diseases report dietary interventions such as fasting, vegan diet, and lactovegetarian diet (25, 54). Clinical dietary therapy studies of AS have focused on some form of dietary elimination such as low starch diet and diet that excludes dairy products (35, 37).

Gut involvement in the pathogenesis of rheumatic diseases was proposed by Smith (55), and more recent studies have investigated this further, suggesting that as the intestinal bacterial flora may be affected by diet, a diet that could influence the intestinal flora might have an effect on disease activity (54, 56). *Klebsiella pneumoniae* was suggested as a trigger for AS and Crohn's disease based on molecular mimicry, and a low starch diet was proposed as a means of reducing *Klebsiella* bacteria in the gut and, hence, further pathological damage (10-13). The gut microbiome can also be altered using probiotics, live bacteria, and yeasts, which are considered as having possible health benefits (57). Animal models have shown that *Lactobacillus*

casei can reduce joint damage in mouse models of arthritis, while HLA-B27 transgenic rats have been shown to be less likely to have a relapse of colitis when given *Lactobacillus rhamnosus GG* (58). However, while one uncontrolled study of probiotics included in this review showed an improvement in BASDAI and VAS scores, two RCTs did not confirm this association (28, 30, 36). Several small trials of probiotics in RA patients have reported marginal, non-significant, beneficial effects on the RA disease activity (59-61). A recent case-control study showed that breastfeeding, which influences microbiota, reduces the risk of the development of AS (62).

A core set of recommendations for patients with AS proposed by Feldtkeller et al. (19) advises a reduction in meat consumption and increase in the consumption of fish and vegetarian meals. In addition, it is recommended that sufficient vitamin D and calcium intake are important to prevent osteoporosis.

Conclusion

In this systematic review, we have determined, from a relatively small number of studies, that the evidence on the relationship between diet and AS is extremely limited and we have highlighted important methodological weaknesses in the studies reviewed.

Many AS patients believe that the aspects of diet affect their symptoms and/or have altered their diets in attempt to improve symptoms. However, well-designed studies of dietary patterns and nutrients are required before any AS-specific recommendations can be made. Future prospective, population-based studies using validated dietary assessment methods should focus on dietary patterns that have been implicated in other inflammatory conditions, including cardiovascular disease, to determine whether diet plays a role in the susceptibility to AS and AS severity.

Clinical and research consequences

- Information on relationship between diet and AS is extremely limited;
- Evidence on a possible relationship between AS and diet is inconclusive;
- There is a need for large population-based epidemiological studies investigating the relationship between AS and diet.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - T.V.M., G.J.M.; Design - T.V.M.; Supervision - T.V.M., G.J.M.; Resources - T.V.M., G.J.M.; Data Collection and/or Processing - J.H., H.M.A.; Analysis and/or Interpretation - T.V.M., G.J.M., K.G.; Literature Search - J.H., H.M.A.; Writing Manuscript - T.V.M., J.H., G.J.M., E.P., K.G.; Critical Review - T.V.M., H.M.A., E.P., K.G., J.H., G.J.M.

Acknowledgements: We are grateful to Professor Alan Ebringer, Professor Bo Abrahamsen and Dr Bjorn Sundström for sending papers for our review.

Conflict of Interest: TVM reports grant from National Ankylosing Spondylitis Society (NASS), during the conduct of the study. GJM reports grant from NASS, during the conduct of the study; and GJM is Chief Investigator of the British Society for Rheumatology (BSR) Biologics Register in Ankylosing Spondylitis. The BSR receives or has received funds for the conduct of this register from Pfizer, AbbVie and UCB. No conflict of interest was declared by the other authors.

Financial Disclosure: This work was supported by the National Ankylosing Spondylitis Society (NASS). JH worked on the project while taking part in an Erasmus student placement under the European Lifelong Learning Programme. HMA received funding from the Higher Committee for Education Development in Iraq (HCED-Iraq) to undertake her PhD.

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