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Recommendations and metaanalyses

Dietary recommendations of the French Society for Rheumatology for patients with chronic inflammatory rheumatic diseases

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ABSTRACT

This article presents the 1st set of dietary recommendations of the French Society for Rheumatology for patients suffering from chronic inflammatory rheumatic diseases (IRD) made by a working group consisting of 12 rheumatology experts, 3 physician nutrition specialists, 1 internal medicine specialist, 1 registered dietician and 3 representatives from patient associations. This group relied on a systematic literature review and on expert opinions, while taking into consideration not only the joint effects of diet in IRD but also the extra-articular ones. Eight general principles and nine recommendations were established. The general principles emphasize that nutritional advice is not a substitute for pharmacological treatment of IRD and that it is an integral part of the patients' overall care, which could help the patient actively participate in their care. The recommendations propose supporting weight loss in subjects who are overweight or obese, a Mediterranean-type diet and supplementation in polyunsaturated fatty acids, mainly omega-3. Conversely, gluten-free diets (in the absence of celiac disease), vegetarian/vegan diets, fasting and elimination of dairy products should not be proposed. Supplementation with vitamins or trace elements is not indicated for controlling chronic IRD activity, while the use of probiotics or spices is not recommended given the limited or disparate data.

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1. Introduction

When caring for patients suffering from chronic inflammatory rheumatic diseases (IRD), non-pharmacological measures are important, as recommended by the French Society for Rheumatology (SFR) [1,2]. In fact, along with medications, these measures help to control the disease activity to improve the patient's overall care. Among non-pharmacological measures, diet could be particularly relevant by modulating the immune and/or inflammatory response and modyfing the cardiovascular risk [3]. As such, dietary measures were mentioned in the recommendations specific to rheumatoid arthritis (RA) [1].

Beyond IRD, diet is a topic that interests the general population; it has been the subject of various studies that have led to dietary and nutritional recommendations for the overall health of the French population (PNNS – French national nutrition and health program) [4,5]. Certain modifications to dietary habits in the French general population in recent years have also been identified, such as increased frequency of exclusion diets such as gluten-free diets (in the absence of confirmed celiac disease) [6] or reduction in the intake of meat and dairy products [7]. While data are sparse, this interest in diet is also observed in patients suffering from chronic IRD who may perceive diet as a "natural" way to improve their IRD on a day-to-day basis. Patients may also perceive that certain foods affect their RA symptoms (improvement or worsening), which may cause them to adopt food avoidance strategies [8].

Thus, patients want specific information about dietary habits to adopt for their chronic IRD. Numerous studies have evaluated different types of interventions (exclusion diets, Mediterranean diet, food supplements, fasting, etc.) and there is plenty of information about them – which has not necessarily been validated – in the popular literature and on social media, sometimes having commercial aims. Conversely, there is little information about the potential harmful effects of unsupervised exclusion diets.

This led us to establish recommendations on diet and dietary habits for patients suffering from chronic IRD intended for health professionals (rheumatologists, physician nutrition specialists, dieticians), under the auspices of the SFR, in partnership with learned societies focused on nutrition [Société française de nutrition (SFN); Société francophone nutrition clinique et métabolisme (SFNCM); Association française d'étude et de recherche sur l'obésité (AFERO); Association française des diététiciens nutritionnistes (AFDN)] and associations for patients suffering from chronic IRD [Association nationale de défense contre l'arthrite rhumatoïde (ANDAR); Association France spondyloarthrites (AFS); Association française des polyarthritiques et des rhumatismes inflammatoires chroniques (AFP^{ric})].

2. Methods

These recommendations were established by following the normalized procedures proposed by the EULAR [9]. A working group designated by the SFR, made up of 12 rheumatology experts, 3 physician nutrition specialists, 1 internal medicine specialist, 1 registered dietician and 3 representatives from patient associations from all over France met to come up with these recommendations. The working group relied on a systematic literature review done by four fellows (J.G.L., Y. N., P. S. and J. Si.) to summarize the data available up to June 2020. This systematic literature review was carried out according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) recommendations [10] using the Medline database (via PubMed) and published abstracts from the 2018–2020 conferences of the EULAR and 2018–2019 conferences of the American College of Rheumatology (ACR). This resulted in the preparation of several articles [11–14]. The objective of this systematic literature review was to answer questions that had been previously validated by the working group. These questions pertained to the following populations: adult patients with RA, spondyloarthritis (SpA) or psoriatic arthritis (PsA). Only randomized, controlled studies were included, with no minimum threshold for the number of patients. Table 1 summarizes the interventions studied. These interventions were evaluated using the following criteria: effectiveness on disease activity and its functional impact, extra-articular manifestations and therapeutic response. The secondary effects and adherence to the various diets/foods were also evaluated. After the data from the scientific literature were presented, the experts were separated into small groups to work on the various general principles and recommendations based on the draft made by C.D., J.Se., RM.F. and S.C. The level of evidence was presented with each proposal [15]. Each item was then presented to the entire working group in its modified version. For an item to be retained, more than 75% of participants

Table 1
Number and quality of the randomized controlled trials for each diet, food, nutrient or dietary practice studied in patients who have a chronic inflammatory rheumatic disease.

Intervention studied	Number of studies	Total number of patients	Quality (Jadad score)[a]
Low-calorie diet and weight loss intervention (including bariatric surgery)	1	138	3
Gluten-free diet[b]	3	185	2–3
Vegetarian/Vegan diet[b]	6	322	2
Fasting[b]	3	92	1–2
Elemental diet	4	124	1–3
Dairy and dairy products	0	0	–
Paleo/Seignalet diet, ketogenic diet, Kousmine diet, diet rich/poor/supplemented in starchy foods (bread, cereals, potatoes, pulses), "acidic" foods (tomatoes, etc.)	0	0	–
High-protein diet	2	71	4
Fishery products, mussels, fish oil, added fat, fatty acids, omega-3	40	2126	1–5
Mediterranean-type diet	5	456	0–3
Vitamins (A, B, C, D, E)	13	1556	1–5
Sweeteners, food additives, "organic" foods	0	0	–
Antioxidants, fruits and vegetables	7	374	1–5
Sweets, beverages (alcohol, coffee, tea)	0	0	–
Fiber/prebiotics, probiotics and synbiotics	10	521	2–5
Minerals (calcium, copper, iron, iodine, magnesium, manganese, phosphorus, potassium, selenium, sodium/salt, zinc)	6	191	0–4
Spices (garlic, turmeric, ginger, cinnamon, saffron, etc.)	6	316	2–5

[a] The Jadad score was used to evaluate the methodological quality of studies, with 0 being the lowest quality and 5 the highest quality.
[b] Combined intervention of fasting, vegetarian/vegan diet, gluten-free diet, fatty acid supplementation.

Table 2
Dietary Recommendations of the French Society for Rheumatology for patients with chronic inflammatory rheumatic diseases.

General principles and recommendations	Level of evidence	Grade	Agreement of working group[a] Mean (SD)	Agreement of review board[a] Mean (SD)
General principles				
A. Nutritional advice is not a substitute for pharmacological treatment of chronic inflammatory rheumatic diseases	NA	NA	9.9 (0.3)	9.8 (0.5)
B. The nutritional advice given to patients affected by chronic inflammatory rheumatic diseases should be based on data from the scientific literature	NA	NA	9.5 (1.0)	9.2 (1.2)
C. Nutritional support is integrated into the overall care of patients affected by chronic inflammatory rheumatic diseases	NA	NA	9.4 (1.2)	9.0 (1.3)
D. Broaching dietary habits can help patients get actively involved in the overall care of their chronic inflammatory rheumatic disease	NA	NA	9.2 (0.9)	8.9 (1.4)
E. The nutritional advice given to patients affected by chronic inflammatory rheumatic disease must take into account the intra- and extra-articular effects, particularly cardiometabolic and bone	NA	NA	9.7 (0.8)	9.5 (0.9)
F. The nutritional advice must take the cultural and socioeconomic context into account	NA	NA	9.3 (1.0)	9.1 (1.2)
G. Nutritional advice is indissociable from the promotion of exercise	NA	NA	9.4 (1.0)	9.1 (1.4)
H. If other nutritional recommendations exist that are specific to a disease, clinical condition or associated treatment, these continue to apply (e.g. undernutrition, obesity, sarcopenia, osteoporosis, etc.)	NA	NA	9.4 (0.9)	9.0 (1.5)
Recommendations				
1. In patients who are overweight or obese, weight loss support should be proposed to control chronic inflammatory rheumatic disease activity; weight loss also has beneficial cardiometabolic and psychological effects		C	9.6 (0.6)	8.5 (1.5)
2. A gluten-free diet should not be proposed as a means to control chronic inflammatory rheumatic disease activity, in the absence of confirmed celiac disease		C	9.8 (0.5)	9.1 (1.3)
3. Fasting or vegan diets should not be proposed to control the activity of chronic inflammatory rheumatic diseases		D	9.7 (0.6)	9.1 (1.8)
4. Eliminating dairy products should not be proposed for managing chronic inflammatory rheumatic disease		C	9.6 (0.7)	9.2 (1.3)
5. Supplementation with polyunsaturated fatty acids, mainly omega-3, of more than 2 g per day, could be proposed for symptomatic relief in patients who have rheumatoid arthritis and likely for those suffering from other chronic inflammatory rheumatic disease		A	8.9 (1.8)	7.9 (2.0)
6. A Mediterranean-type diet could be proposed to patients who have rheumatoid arthritis and likely to those affected by other chronic inflammatory rheumatic disease given its effects on joint symptoms and foremost the cardiometabolic diseases		C	8.8 (2.1)	8.5 (1.7)
7. To control the activity of chronic inflammatory rheumatic diseases, there is no indication for proposing vitamin (B9, D, E, K) or trace element (selenium and/or zinc) supplementation		B	9.6 (0.9)	8.4 (2.1)
8. Given that the data on the effectiveness of probiotics is insufficient and disparate, they are not recommended for controlling chronic inflammatory rheumatic disease activity		B	9.4 (0.6)	8.6 (1.8)
9. Certain supplements (saffron, cinnamon, garlic, ginger, sesamin, pomegranate concentrate) could have beneficial effects on rheumatoid arthritis disease activity but the data are currently too limited to propose their use in current practice		B	9.2 (1.1)	8.1 (2.1)

The recommendation grade reflects the level of evidence: a corresponds to the highest level of evidence, NA: not applicable.
[a] Agreement score between 0 and 10 where 10 is complete agreement.

had to be in favor of it. The item was discussed and reformulated if needed, then a 2nd vote was taken, with a score ranging from 0 to 10, where 0 corresponded to complete disagreement with the recommendation and 10 indicating complete agreement. When a consensus was achieved (> 75% of participants giving a score ≥ 8) the item was validated. A 3rd vote was taken by email in the week following the meeting. The results of this vote are shown in Table 2.

The recommendations were then reviewed by a review board made up of 51 experts (rheumatologist practicing at a hospital or in private practice, physician nutrition specialist practicing at a hospital or in private practice, registered dieticians). The members of this review board voted on a scale of 0 (completely disagree) to 10 (completely agree). Their comments were considered when writing the text that accompanied the recommendations. The results of this vote are also shown in Table 2.

3. Results

This process resulted in the declaration of eight general principles and nine recommendations (Table 2). The level of evidence, recommendation grades and strength of agreement of the working group and review board are also given in Table 2 for each recommendation.

3.1. General principles

Principle A: Nutritional advice is not a substitute for pharmacological treatment of chronic inflammatory rheumatic diseases.

It is crucial to start with this first general principle in any discussion with a patient about their diet. In fact, the level of evidence of studies on dietary changes or nutritional supplements is limited, while the interventions that have been studied the most show only a modest effect on symptoms. It is important to emphasize that none of these studies have shown a structural effect. Nutritional advice can thus only be considered as a supplement to pharmacological treatment; it must not delay or replace standard treatments with medications.

The term "nutritional advice" was chosen for most of the general principles. The working group determined that nutritional advice was the result of a discussion with the patient and did not consist of a medical prescription, which seems relevant considering the interventions proposed and the modest effects observed.

Principle B: The nutritional advice given to patients affected by chronic inflammatory rheumatic diseases should be based on data from the scientific literature.

Several beliefs conveyed by different actors (social media, food-processing industry, caregivers, patients, etc.) circulate on the links between diet and IRD. The working group felt it was important to remember that advice given by doctors to patients must be based on scientific data, whereas there is plenty of information in plain-language medical websites, social networks and the internet that do not have sufficiently robust scientific evidence to justify their application in daily practice. The purpose of these recommendations is, among others, to recall the currently available data to help healthcare professionals in their discussions with patients. Obviously, these recommendations could eventually change as our knowledge expands.

Principle C: Nutritional support is integrated into the overall care of patients affected by chronic inflammatory rheumatic diseases.

Diet is a very important factor for health in general. It is one of the main determinants of the composition of our gut microbiota, which can itself impact health though local modifications (gut permeability, gut immunity) or more systemic ones (stimulation of nerve endings and gut–brain axis, systemic release of microbiota-derived metabolites, hormones, antigens, etc.) [16–18]. Diet affects cardiovascular risk, cancer risk, mood, etc. [19]. The purpose of this general principal is to motivate doctors who care for patients affected by IRD to become interested in this topic. While data in IRD is still limited, it appears important to listen to patients' feel and their dietary habits. The 2018 update of the SFR recommendations on RA and SpA management already emphasized the need for overall care of patients, with nutritional advice included within non-pharmacological measures [1,2].

Principle D: Broaching dietary habits can help patients get actively involved in the overall care of their chronic inflammatory rheumatic disease.

We know how important it is for patients to play an active role in their health. Patient education is an important tool for making this happen. It is widely recommended in the overall care of patients affected by IRD [20]. Changing how one eats is also a means for patients to actively participate in treating their disease, beyond medication compliance. Getting involved in one's care empowers patients and develops self-efficacy, which can have beneficial effects on physical health and coping ability [21].

Principle E: The nutritional advice given to patients affected by chronic inflammatory rheumatic diseases must take into account the intra- and extra-articular effects, particularly cardiometabolic and bone.

While the level of evidence of studies on how diet affects joint symptoms is limited and the observed effects are modest, it is important to consider nutritional advice that also takes into consideration the extra-articular manifestations of these interventions. In fact, patients with IRD are at increased risk of cardiovascular events and death, along with increased risk of osteoporosis due to chronic inflammation and use of certain treatments [22]. These extra-articular components carried weight in the risk/benefit ratio that was evaluated when coming up with the different recommendations.

Principle F: The nutritional advice must take the cultural and socioeconomic context into account.

It is important to remember that these recommendations cannot be considered without context. Of course, clinicians must take into account different factors specific to the patient, such as the cultural and socioeconomic context, to adapt their discussions. It is also important to remember that eating is a source of pleasure and social interaction and that exclusion diets can have a negative psychosocial impact, in addition to the risk of deficiencies.

Principle G: Nutritional advice is indissociable from the promotion of exercise.

This work does not encompass physical activity. Thus, we did not make any recommendations on this topic. However, it was apparent to the working group that promoting exercise was an important part of the nutritional support, particularly for a weight loss goal. Some believe that exercise is also an element of the Mediterranean diet. The development of specific recommendations about exercise in IRD was placed on the research agenda (Box 1).

Box 1 : Research agenda

Draw up recommendations on exercise in IRD

Draw up recommendations on the detection and treatment of undernutrition, sarcopenia, overweight and obesity in IRD

Evaluate the impact of weight loss (medical or surgical) on IRD activity through new high-quality studies

Evaluate the impact of dietary interventions on patient-related outcome measures

Evaluate the impact of a gluten-free diet, lactose/dairy-free diet using an exclusion diet design in both groups with addition of gluten/lactose vs. placebo through new high-quality studies

Evaluate the impact of intermittent fasting through new high-quality studies

Evaluate the impact of organic foods or highly processed foods on the activity of rheumatic diseases through new high-quality studies

Evaluate the impact of preventive dietary interventions in subjects at high risk for rheumatic diseases

Study the link between the response to dietary changes and the gut microbiota in patients with IRD

Principle H: If other nutritional recommendations exist that are specific to a disease, clinical condition or associated treatment, these continue to apply (e.g., undernutrition, obesity, sarcopenia, osteoporosis, etc.).

This general principle was proposed to highlight the fact that these recommendations must not prevail over those that could be issued in other clinical situations where the proposed nutritional interventions have a higher level of evidence. After discussion, the working group determined that in most cases, these recommendations do not go against the nutritional recommendations issued for other clinical conditions. Thus, the initial proposal which was "the other specific nutritional recommendations prevail" was replaced by "continue to apply". Celiac disease, which was initially listed, was removed since recommendation 2 on gluten-free diets already states "in the absence of confirmed celiac disease". Obviously, the proposed list is not exclusive. We can add gout – a joint condition in which dietary measures have a proven impact and are an integral component of the treatment recommendations [23] – heart failure, kidney failure, irritable bowel disease flare-ups, etc. The decision to list undernutrition, obesity, sarcopenia and osteoporosis was made because it appeared to the working group that these conditions were often present concurrently with IRD. Detection and treatment of undernutrition and sarcopenia in patients with IRD could be the subject of a specific discussion and recommendations, thus was included in the research agenda (Box 1).

3.2. Recommendations

Recommendation 1: In patients who are overweight or obese, weight loss support should be proposed to control chronic inflammatory rheumatic disease activity; weight loss also has beneficial cardiometabolic and psychological effects.

Only one randomized controlled trial on patients suffering from PsA was found during the systematic literature review [24]. In that study, 138 overweight or obese patients starting TNF inhibitor therapy were randomized into two arms: calorie-restricted diet (about 30% of total energy needs) or no restrictions on eating. Minimal disease activity (MDA) was reached more often by the patients in the low-calorie diet than by the others (hazard ratio = 1.85 [95% CI: 1.019–3.345]). Patients who lost more than 5% of their bodyweight, independent of which arm they were assigned to, had a 4-fold greater likelihood of achieving MDA than the others (odds ratio = 4.20 [1.82–9.66], $P < 0.001$).

Outside randomized trials, several studies have shown a link between obesity and the severity of IRD [25,26]. Observational studies also suggest a beneficial effect of weight loss (through calorie reduction or bariatric surgery) on RA and PsA disease activity [27–30]. Randomized controlled trials also found a beneficial effect of weight loss through dieting on psoriasis [31].

Moreover, being overweight is associated with increased risk of cardiovascular events, depression and cancer; their reduction is a major objective of France's health advisory council (Haut Conseil de la Santé Publique – HCSP). Note that in observational studies, weight loss is associated with increased mortality in patients with RA and other chronic diseases. This paradox can likely be explained by the fact that the weight loss itself is related to the underlying chronic disease, contributing to mortality [32].

The detection of overweight and obesity in IRD was not taken up in these recommendations. Like sarcopenia and undernutrition, the detection of overweight and obesity in patients affected by IRD could be the subject of specific discussions and recommendations. It was also added to the research agenda (Box 1).

Recommendation 2: A gluten-free diet should not be proposed as a means to control chronic inflammatory rheumatic disease activity, in the absence of confirmed celiac disease.

A gluten-free diet is becoming more widespread in the general population for its supposed beneficial effects on health (apart from celiac disease) [6]. This may also be the case in patients affected by IRD. Some patients report that their symptoms improved after they eliminated gluten from their diets [33]. No randomized study has looked at the effects of a gluten-free diet alone. Two randomized controlled studies combined a gluten-free diet with a vegan diet [34,35], with or without prior fasting [36]. The outcomes were evaluated by an independent observer in the first study and open in the other. The diet was followed for 1 year and for 3.5 months, respectively (preceded by a 10-day fast). A large portion of the patients in the "intervention" group dropped out from the study before it ended [42% (16/38) and 37% (10/27), respectively]. Note that these are old studies in which patients were not optimally treated (no information about the type of treatment in the first study and no methotrexate in the second). In the first study, the effectiveness was only determined in the patients who finished the study (per protocol analysis), which greatly limits the conclusions, in a population that bears little resemblance to the current patient population. In the subgroup of patients who finished the study, the changes in DAS28 were greater in the intervention group [DAS28 went from 5.3 to 4.3 ($P < 0.001$) and 5.3 to 5.0 ($P = 0.19$), respectively, in the intervention and control groups]. In the second study, where an intention to treat analysis was done, the number of painful and swollen joints was less during the follow-up period in the intervention group. Nevertheless, it is important to note that on average, patients in the intervention group still had 18 painful joints and 8 swollen joints, thus they were not anywhere near the current treatment target for RA (remission or low activity). Also, structural progression was observed in both groups. In these two studies, the patients in the "intervention" group lost a significant amount of weight (mean ≈ 4.2 and 6 kg, respectively), contrary to patients in the control groups (mean ≈ 0.7 and 0 kg, respectively). This weight loss could, at least in part, explain the observed effect.

A double-blind French study with a gluten-free diet in both arms and the addition of products that contain gluten or not, is on-going for SpA but not in RA (research agenda) [37].

Beyond the effects on joint symptoms, the cost of gluten-free products is on average double that of the standard corresponding foods and following a strict gluten-free diet may have impact on patient's lives socially [38,39]. Moreover, two American cohort studies suggest that, in the general population, the consumption of gluten could be associated with a reduction in the occurrence of cardiovascular events and diabetes. Given that the cardiovascular risk in patients with IRD is increased and the data on joint symptoms for a gluten-free diet are insufficient and open to criticism, proposing a gluten-free diet to patients with IRD is not recommended [37].

Recommendation 3: Fasting or vegan diets should not be proposed to control the activity of chronic inflammatory rheumatic diseases.

Three controlled studies have been done on the effect of fasting in RA: one with a short-term assessment of a 7-day fast in 13 patients (crossover study) [40] and two with a 7–10 day fast followed by lactovegetarian diet for 9 weeks [41] ($n = 26$) or gluten-free vegan diet for 3.5 months then lactovegetarian diet for 9 months [36] (study described in the previous section, $n = 53$). The first study found a short-term beneficial effect of fasting but provided no information about the maintenance of the joint effects once eating had resumed [40]. The second study found a beneficial effect of fasting in 5 of 15 patients but it was not maintained during the period in which the lactovegetarian diet was followed. In the study by Kjelsen-Kragh et al., the beneficial joint effect was achieved at the end of the fasting period and the vegetarian diet was able to maintain this effect without providing additional benefit [36]. Nevertheless, here again, a per protocol analysis was done, which did not include the large number of patients who dropped out (10/27 in the intervention group and 9/26 in the control group), which makes the results difficult to interpret.

Two studies in patients suffering from RA combined a vegetarian diet with either fish oil high in omega-3 [42] or drinks rich in *Lactobacillus* [43]. In the groups that did not receive omega-3 supplementation in the first study, only the pain level on VAS improved in the vegetarian diet relative to the Western diet [no effect on the number of painful or swollen joints, nor on the Health Questionnaire Assessment (HAQ)] [42]. The other study found no significant effect of a vegetarian diet on parameters of RA disease activity [43].

Thus, data on vegetarian or vegan diets do not suggest any relief of joint symptoms, and while an extended 7-day fast may have beneficial effects, these do not appear to be maintained once the subject starts eating again, which considerably limits is relevance. It is important to remember that extended fasting must be supervised strictly by a health care practitioner and the patients must be informed of the risks incurred. Structural effectiveness of this type of diet has not been demonstrated. Other variations of shorter fasts, such as intermittent fasting, have not been evaluated in IRD (research agenda).

Recommendation 4: Eliminating dairy products should not be proposed for managing chronic inflammatory rheumatic disease.

The belief that dairy products have harmful effects is widespread in society, and their consumption in France has decreased in recent years [7]. Nevertheless, no study has supported this hypothesis in IRD. Again, the only relevant data comes from the study by Kjelsen-Kragh et al.: reintroduction of dairy products after the vegan diet period did not alter the joint symptoms [36]. To our knowledge, no other controlled study in humans or animals has been done on the effects of dairy products, or their elimination, in IRD. The intestinal mucosa of RA patients is not hyper-reactive to cow's milk proteins and there was no correlation between the intolerance felt by patients and the reactivity of their intestinal mucosa [44].

Dairy products are the main dietary source of calcium. Patients with IRD have a higher risk of developing osteoporosis because of the nature of their disease and the frequent and prolonged exposure to corticosteroids. A recent meta-analysis confirms the beneficial effects of 12 to 24 months of calcium supplementation on bone mineral density, particularly in countries where dietary intake of calcium is low [45]. Another meta-analysis of cohorts reports a protective effect of high intake of dairy products on the risk of hip fracture, with a 13% reduction in risk (relative risk RR = 0.87 [95% CI: 0.76–1.00]) [46]. This reduction in fracture risk was observed with fermented dairy products (RR = 0.75 [0.66–0.86] and RR = 0.68 [0.61–0.77] for yogurt and cheese, respectively) but not with milk (RR = 0.91 [0.74–1.12]). However, this study was criticized because of the large variability in how different studies defined consumption categories, leading to potential classification bias and numerous potential confounding factors [47]. Furthermore, fermented dairy products also appear to have cardiovascular benefits. A recent meta-analysis of 20 cohort studies found a 4% reduction in cardiovascular events (stroke, myocardial infarct, ischemic cardiopathy, sudden cardiac death) (RR = 0.96 [95% CI: 0.94–0.98] associated with consumption of fermented dairy products, along with a 27% reduction in the risk of type 2 diabetes (RR = 0.73 [0.70–0.76] and 20% reduction in the risk of metabolic syndrome (RR = 0.80 [0.74–0.87]) associated with the consumption of yogurt [48]. The Multi-Ethnic Study of Atherosclerosis 5MESA) study, which followed the progression of coronary artery calcifications by coronary CT angiography in 5273 participants, found a protective effect of consuming whole milk with lower cardiac calcium score at enrollment and slower progression during the follow-up period after adjusting for multiple factors (OR = 0.765 [0.60–0.98]) [49]. Thus, the working group proposed following the recommendations set out for the general population by the PNNS, which is two servings of dairy products per day for adults. It may be interesting to favor consuming fermented dairy products, which are easily digested and could provide greater beneficial extra-articular effects.

Recommendation 5: Supplementation with polyunsaturated fatty acids, mainly omega-3, of more than 2 g per day, could be proposed for symptomatic relief in patients who have rheumatoid arthritis and likely for those suffering from other chronic inflammatory rheumatic diseases.

The term "essential polyunsaturated fatty acids" (PUFA) refers to the large families of omega-3 (mainly found in the fish and marine algae oils) and omega-6 (mainly found in vegetable oils). These are labelled as essential since they are needed by the body but cannot be synthesized by it; they can only be provided by exogenous sources. Contrary to other recommendations, this one is based on extensive literature data with, at the time of the literature search, 43 randomized placebo-controlled trials and several meta-analysis studies, which justifies a grade A recommendation. The literature review that was done for the development of these recommendations made it possible to conduct a new meta-analysis grouping 31 of these studies and capturing 1464 patients affected by IRD [13].

Most of these studies were done on patients suffering from RA (26 of the 31 studies; 1014 of the 1464 patients) thus the recommendation is focused on this population. PUFA supplementation led to a significant decrease in all the clinical parameters studied, with a large effect in the VAS activity, moderate on VAS pain, the DAS28 and the HAQ, and a weak effect on morning stiffness. It also leads to significant reduction in the erythrocyte sedimentation rate (ESR), but not in C-reactive protein (CRP). Furthermore, most studies involved 3 to 6 months of supplementation. The analyses after 1 month found no significant effect, suggesting that supplementation must last at least 3 months. There is no data on the maintenance of the beneficial effects after the end of supplementation or how often the treatment courses should be repeated. As for the dose, the working group decided to specify that supplementation with at least 2 g per day of PUFA is preferred. While the meta-analysis found no difference in the effect on joint symptoms relative to the dose used, the literature overwhelmingly features supplementation of at least 2 g per day (25 of the 29 studies specified the dose used). Data on supplementation with less than 2 g per day was found in a limited number of patients ($n = 224$). Most of the studies revolve around omega-3 supplementation and less frequently on other PUFAs (omega-6, omega-9). Moreover, while the data are only based on a few studies and are subject to discussion, a recent meta-analysis suggests a protective effect of PUFA supplementation on the risk of cardiovascular events only at doses of 2 g per day or more [50].

As for the source of the PUFAs, the literature mainly focusses on omega-3 from animal sources, since 23 of the 31 studies included in the meta-analysis were on fish oils [mainly contributing eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)]. Thus, this source is likely preferable.

In practice, one can propose supplementation by capsule, favoring fish oils (mainly EPA and DHA) with dosages of 2–3 g/day for 3 to 6 months, which will be reevaluated based on the effects observed by the patient. Supplementation with higher doses or for very long durations were associated with an increased risk of bleeding, thus it is preferable to follow these dosages and prescription duration [51,52]. To date, there is no data on the prescription of repeated courses, thus it is difficult to propose a frequency or number of courses to use when the patient feels beneficial effects. We should also encourage patients to increase their intake of PUFAs (mainly omega-3) from foods, particularly by adopting a Mediterranean-type diet (recommendation 6).

> Recommendation 6: A Mediterranean-type diet could be proposed to patients who have rheumatoid arthritis and likely to those affected by other chronic inflammatory rheumatic diseases given its effects on joint symptoms and foremost the cardiometabolic diseases.

Five randomized controlled trials on the effect on joint symptoms of a Mediterranean diet in IRD have been conducted: three in Scandinavian countries, one in England and one in Mexico [53–57] (Table S1) [See the supplementary material associated with this article online]. Three were open and two had an independent observer. The quality of the methodology was mediocre (Jadad score between 0 and 3). The term "Mediterranean-type diet" can encompass different realities that adapt to the sociocultural context; the details of these interventions are described in Supplemental Table 1. Along with the dietary changes, one study provided probiotics [53] and another prescribed a formal exercise program [57]. Three studies found a significant improvement in the joint symptoms [54–56], one study found no difference between the control and intervention arms, although both arms received a formal exercise program [57]. Lastly, the final study found no significant improvement in the main endpoint analyzed using a linear mixed-effects model; however the DAS28-ESR was significantly reduced during the intervention periods relative to the control periods in non-adjusted analysis (crossover study) [53]. While the few studies on this topic have mediocre quality, there is evidence in favor of a beneficial effect on joint symptoms for a Mediterranean-type diet in RA.

Moreover, the PREDIMED primary prevention study of 7447 subjects at high cardiovascular risk showed about a 30% reduction in major cardiovascular events with a Mediterranean-type diet supplemented with olive or nut oil relative to a low-fat diet [58].

Thus, the working group felt it was important to propose a Mediterranean-type diet in patients affected by IRD, primarily for its cardiometabolic effects and potentially for its effects on joint symptoms. Note that this recommendation is consistent with the recommendations of the PNNS (Table S1).

> Recommendation 7: To control the activity of chronic inflammatory rheumatic disease, there is no indication for proposing vitamin (B9, D, E, K) or trace element (selenium and/or zinc) supplementation.

The systematic literature review done to support the conclusions of the working group on the use of vitamin supplements in IRD was published elsewhere [11]. Thirteen randomized controlled trials have been done, all in RA: eight on vitamin D, two on vitamin E, two on folic acid (vitamin B9) and one on vitamin K. The studies on vitamin K, folic acid, vitamin D (meta-analysis of two studies) and on vitamin E (meta-analysis of two studies) found no significant effect on joint symptoms. A preliminary study in 15 RA patients had suggested a beneficial effect of selenium supplementation [59]; however its findings were refuted by other studies on large sample sizes [60,61]. Two trials with small sample sizes found no significant joint effects in RA patients of zinc supplementation [62,63]. Thus, there is no reason to prescribe vitamins (D, E, B9, K), selenium or zinc for joint symptoms. Vitamin D supplementation continues to have a role in preventing or treating fracture risk in case of deficiency. In the same way, use of folic acid in addition to methotrexate is not challenged.

> Recommendation 8: Given that the data on the effectiveness of probiotics is insufficient and disparate, they are not recommended for controlling chronic inflammatory rheumatic disease activity.

Nine randomized controlled trials have been conducted on probiotics in chronic IRD. In RA, three studies found beneficial effects on joint symptoms [64–66], one study found a significant difference in univariate analysis only [53] and three found no significant effect [67–69] (SLR performed [14]). Among the positive studies, one used strains of *Lactobacillus (L.) casei* for 8 weeks and the other two used *L. acidophilus, L. casei* and *Bifidobacterium (B.) bifidum* also for 8 weeks. The number of colony forming units (CFU) was in the order of 10^8 to 10^9 CFU/strain/day. In SpA, the two available studies (197 patients total) are negative [70,71]. Since the studies used different strains for various durations and the results were heterogeneous, it is currently difficult to make broad conclusions about their efficacy in IRD, and thereby to recommend they be prescribed. The working group has chosen to specify in its recommendation that "current" data were insufficient and disparate, so as to not completely rule out the role of probiotics, especially in RA.

Recommendation 9: Certain supplements (saffron, cinnamon, garlic, ginger, sesamin, pomegranate concentrate) could have beneficial effects on rheumatoid arthritis disease activity but the data are currently too limited to propose their use in current practice.

Our systematic literature review revealed a certain number of recent studies with good methodological quality that found a beneficial effect on joint symptoms in RA patients. Thus, several spices or supplements could have clinically significant beneficial effects [12]. This is the case for saffron (1 study, 66 patients, 100 mg/day) [72], cinnamon (1 study, 36 patients, 2 g/day) [73], garlic (1 study, 70 patients, 1 g powder ≈ 2.5 g fresh garlic/day) [74], ginger (1 study, 63 patients, 1.5 g powder/day) [75], sesamin (1 study, 44 patients, 200 mg/day) [76] and pomegranate concentrate (1 study, 55 patients, 500 mg/day) [77]. These spices have been used for several thousands of years in Asia because of their anti-inflammatory properties. Nevertheless, while the results of the above studies appear interesting, they are too preliminary to recommend the use of these spices and supplements in practice. We also do not know if spices mixed into food and cooked at typical doses have the same properties as the encapsulated spice concentrates tested in these studies. Thus, the working group has chosen to list potentially relevant supplements using the conditional to facilitate the discussions with patients about existing studies, without going as far as recommending them. Note that other studies, namely on turmeric, have been done but their quality was not sufficient to be cited in the recommendation [78,79].

4. Discussion

The arrival of targeted therapies revolutionized the treatment of IRDs. However, the care of patients with IRD should be comprehensive and not restricted to solely pharmacological measures. Diet is an integral part of the life of individuals whether or not they have IRD and is closely linked to their health [80]. Thus, altering their diet could be a means for them to impact their disease in this overall approach.

These recommendations consist of eight general principles and nine recommendations. They are based on a systematic literature review done specifically for this project in order to analyze and summarize published scientific data [11–13]. This is actually the subject of one of the general principles (principle B). We have observed that, for certain interventions, sometimes seen as successful by patients (fasting, gluten-free diet, etc.), the data taken from controlled clinical trials are tenuous and often of poor quality. For this reason, certain food exclusion diets (gluten-free, no dairy products, vegetarian, vegan, fasting) were not recommended, while acknowledging that it is necessary to conduct high-quality studies to decide on their role in controlling IRD activity (research agenda). Other diets such as the ones described by Kousmine and Seignalet or other Paleo diets, despite the intensive promotional activities associated with them, have not been the subject of any randomized controlled trials in IRD. Consequently, these diets are not recommended.

Along with the principle on the importance of relying on scientific data, the other general principles were used to place the nutritional advice detailed in these recommendations into the appropriate context. On one hand, this contextualism is centered on the patient and their IRD (nutritional advice only considered as a supplement to pharmacological treatment, nutritional advice that allows patients to be involved in their care, articular and also extra-articular effects of the nutritional interventions, consideration of the concurrent health conditions that justify specific nutritional recommendations and the benefits on combining exercise with nutritional advice). On the other hand, this is an integration of nutritional advice into a patient's day-to-day life within their family, social and professional environment.

The positive recommendations are those about omega-3 supplements and the Mediterranean-type diet. While no current national or international recommendation on the treatment of IRD proposes routine supplementation with omega-3, the depth and quality of the literature on essential PUFA led us to formulate a specific grade A recommendation, in contrast to the daily practice of rheumatologists. Of note, such supplements are not reimbursed in France. The intake of Omega-3 can be in the form of dietary supplements or by following a Mediterranean-type diet. These recommendations are particularly relevant in patients who want to act on their IRD through diet or natural supplements, in combination with their drug treatments, and in patients who have residual subjective symptoms (joint pain, morning stiffness) despite their primary long-term therapy [81].

Several recommendations are negative, i.e., they recommend not taking certain nutrients (vitamins, trace elements, etc.) or not adopting certain diets (gluten-free, fasting, vegetarian, vegan) to control IRD activity. This is justified by the fact that the scientific data do not show the benefits of these dietary interventions for a given objective, or because the scientific data are insufficient or low quality. In these studies, food exclusion diets are often the reason that patients drop out, evidence that these diets are difficult to follow over long periods of time [34–36].

The research agenda mentions themes to dig deeper into, which will help to increase our knowledge and could eventually result in these recommendations being changed. In fact, it is important not to go directly from scientific data generated in experimental cell culture or animal studies to clinical practice without first doing controlled clinical trials.

While certain food exclusion diets are not recommended here, some patients will follow them or ask their doctors about them. For patients who want to or have already followed a food exclusion diet, it is vital to support them, ideally with the help or the supervision of a dietician. One of the first steps is to encourage patients to record the foods they consume so they can see if they are associated with joint symptoms. In patients who already follow an exclusion diet, we can discuss with them whether they have seen any beneficial effects. One can propose gradual reintroduction of certain foods to determine if it makes the symptoms worse. In case of a gluten-free diet, we recommend the consumption of fiber, by proposing food such as quinoa, wild rice, legumes, artichokes, nuts and grains, etc. In case of dairy-free diets, we can recommend the consumption of products high in calcium such as red or white beans, broccoli, spinach, cabbage, high-calcium tofu, sardines with bones, calcium-rich mineral water, etc. In case of vegetarian/vegan diets, we can make sure the patients have sufficient intake of protein, iron, vitamin B12, zinc and calcium; supplementation may be necessary. In all, it is useful to remind patients of the risk of social isolation when one is on a restrictive diet [82] while meals are an important event in many cultures because of the social interaction and associated pleasure [83].

Other than the quality of the scientific literature on the subject of diet and IRD activity, another limitation is the lack of data about the effect of diet on patient-reported outcomes, especially fatigue. Determining the effect of nutritional advice on these parameters would be a major advance in the knowledge about diet during IRD (research agenda). Lastly, there may be large inter-individual differences in the sensitivity of patients to diet, which would limit the conclusions of these studies. In fact, one of the mechanisms by which diet acts on the immune system is by altering the gut microbiota. The composition of the gut microbiota is subjected to large inter-individual variability (80–90%), much more than the human

genome (0.01%) [84,85]. Thus it will be important to study the interaction between the response to dietary changes and gut microbiota in patients suffering from IRD (research agenda) in the same manner that the interactions between disease-modifying antirheumatic drugs (DMARDs) response and gut microbiota are being studied [86].

In France, there are dietary recommendations for the general population provided by the PNNS, which is a public health plan that aims to improve the health of the population by acting on nutrition, given that good nutrition is a protective factor for health [5]. The recommendations made here agree with the nutritional advice from the PNNS, which promotes eating in a way consistent with the Mediterranean-type diet.

5. Conclusion

To conclude, these are the first national and international recommendations on diet in patients affected by chronic IRD. It will be important to update them regularly given how quickly the literature on this subject changes and expands.

Disclosure of interest

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Appendix A. Supplementary data

Supplementary data (Table S1) associated with this article can be found, in the online version, at https://doi.org/10.1016/j.jbspin.2021.105319.

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