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THE ROLE OF DIET IN THE DEVELOPMENT AND TREATMENT OF RHEUMATIC DISEASES IN CHILDREN

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ABSTRACT. There is a fairly large number of publications in the modern Russian scientific literature on the role of diet in the development and course of both rheumatic diseases in adults and various chronic diseases in children. At the same time, the issues of diet therapy of rheumatic diseases in children are practically not discussed in modern Russian-language scientific publications. The only Russian-language scientific article devoted to the diet therapy of juvenile arthritis was published more than 20 years ago. The review of foreign publications on the role of diet in the development and treatment of various rheumatic diseases in children, namely juvenile idiopathic arthritis, juvenile systemic lupus erythematosus, juvenile dermatomyositis, IgA vasculitis, Kawasaki disease and familial Mediterranean fever, is presented. Most of the studies were conducted with patients suffering from juvenile idiopathic arthritis and concerned the role of gluten-free, low-calorie ketogenic, specific carbohydrate diets, intestinal microbiota and enteral nutrition in its treatment, assessment of nutritional status in juvenile idiopathic arthritis, the influence of parental eating behavior, maternal nutrition during pregnancy and nutrition of the child in the first year of life on risks of developing juvenile idiopathic arthritis.

KEYWORDS: *diet therapy, rheumatic diseases, children*

РОЛЬ ДИЕТЫ В РАЗВИТИИ И ЛЕЧЕНИИ РЕВМАТИЧЕСКИХ ЗАБОЛЕВАНИЙ У ДЕТЕЙ

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РЕЗЮМЕ. В современной отечественной научной литературе имеется достаточно большое количество публикаций, посвященных роли диеты в развитии и течении как ревматических заболеваний у взрослых, так и различных хронических заболеваний у детей. При этом вопросы диетотерапии ревматических заболеваний у детей в современных русскоязычных научных публикациях практически не обсуждаются. Единственная русскоязычная научная статья, посвященная диетотерапии ювенильных артритов, была опубликована более 20 лет назад. В настоящей статье представлен обзор зарубежных публикаций, посвященных роли диеты в развитии и лечении различных ревматических заболеваний у детей, а именно ювенильного идиопатического артрита, ювенильной системной красной волчанки, ювенильного дерматомиозита, IgA-васкулита, болезни Кавасаки и семейной средиземноморской лихорадки. Большинство исследований было проведено с участием пациентов, страдающих ювенильным идиопатическим артритом, и касались роли безглютеновой, низкокалорийной кетогенной, специфической углеводной диеты, кишечной микробиоты и энтерального питания в его лечении, оценки нутритивного статуса при ювенильном идиопатическом артрите, влияния пищевого поведения родителей, питания матери во время беременности и питания ребенка на первом году жизни на риски развития ювенильного идиопатического артрита.

КЛЮЧЕВЫЕ СЛОВА: *диетотерапия, ревматические заболевания, дети*

INTRODUCTION

The etiology of the vast majority of rheumatic diseases remains unknown, and drug therapy does not always provide stable remission. New possible theories of the origin of autoimmune rheumatic diseases and various methods of alternative and complementary medicine in their treatment continue to be studied. The Russian scientific literature contains a large number of publications on the role of diet in adult patients with gout and rheumatoid arthritis [1–4]. A large number of Russian-language scientific articles are also devoted to diet therapy of various chronic diseases in children, most of which concern gastrointestinal diseases [5, 6]. However, there are also a sufficient number of modern publications devoted to the effectiveness of a gluten-free diet of autism spectrum disorders [7], efficiency of a ketogenic diet of epilepsy [8], and nutritional features of cerebral palsy and other neurological disorders [9]. Issues of diet for rheumatic diseases in children have been practically not discussed in Russian publications in recent years. The only Russian-language scientific article devoted to diet therapy of juvenile arthritis was published more than 20 years ago [10]. More modern publications on this topic, as well as studies devoted to the role of diet in the development and treatment of other rheumatic diseases in children, were not found in the available Russian-language literature.

AIM

The aim of the study is to review foreign publications on the role of diet in the development and treatment of rheumatic diseases in children.

MATERIALS AND METHODS

A search was performed in the PubMed database for articles published for all time up to April 28, 2024.

On request of "diet, juvenile idiopathic arthritis" were found 94 articles in total. Of these, 34 articles did not address the effects of diet on the development and course of juvenile idiopathic arthritis (JIA), and 23 articles were devoted to other diseases. Also, the full text of 10 articles from 1964–1989 was unavailable, the results of 8 studies from 1990–2000 were presented in a Russian-language review published in 2003 [10] and were not analyzed separately within the framework of this review, and 19 articles from 2003–2024 were included in the review [11–29].

On request of "diet, juvenile systemic lupus erythematosus" 13 articles were found, 5 of them did not concern the influence of diet on the development and course of juvenile systemic lupus erythematosus (JSLE), 3 articles were devoted to other diseases, 5 articles from 2009–2021 were included in the review [20, 27, 30–32]. Among them, 2 articles concerned not only JSLE, but also JIA, and were found using the previous request [20, 27].

On request "diet, juvenile dermatomyositis" 19 articles were found, 5 of them did not address the effects of diet on the development and course of juvenile dermatomyositis (JDM), 8 articles were devoted to other diseases. Full text of 4 articles from 1967–1984 was unavailable, 2 articles from 2016 and 2020 were included in the review [27, 33]. Among them, one article was devoted to JDM, JIA and JSLE and, accordingly, was also found using two previous requests [27].

On request "diet, child, vasculitis" 48 articles were found, of which 11 articles were on systemic vasculitis in children, but did not address the effects of diet on their development and course, 23 articles were devoted to other diseases or systemic vasculitis in adult patients. Among them, one publication was devoted to the clinical observation of a positive response to gluten-free diet in uveitis in a nine-year-old girl with celiac disease and type 1 diabetes mellitus. Full text of 8 articles from 1969–1984 was unavailable, 4 articles devoted to IgA vasculitis, 2019–2021 [34–37], 2 articles devoted to Kawasaki disease, 2013–2016 were included in the review [38, 39].

On request "diet, child, familial Mediterranean fever" 13 articles were found, 8 articles did not concern the influence of diet on the development and course of familial Mediterranean fever (FMF). Full text of 3 articles from 1964–1995 was unavailable, 2 articles from 2020 and 2021 were included in the review [40–41].

The summary results of the search, inclusion, and exclusion of articles are shown in Figure 1.

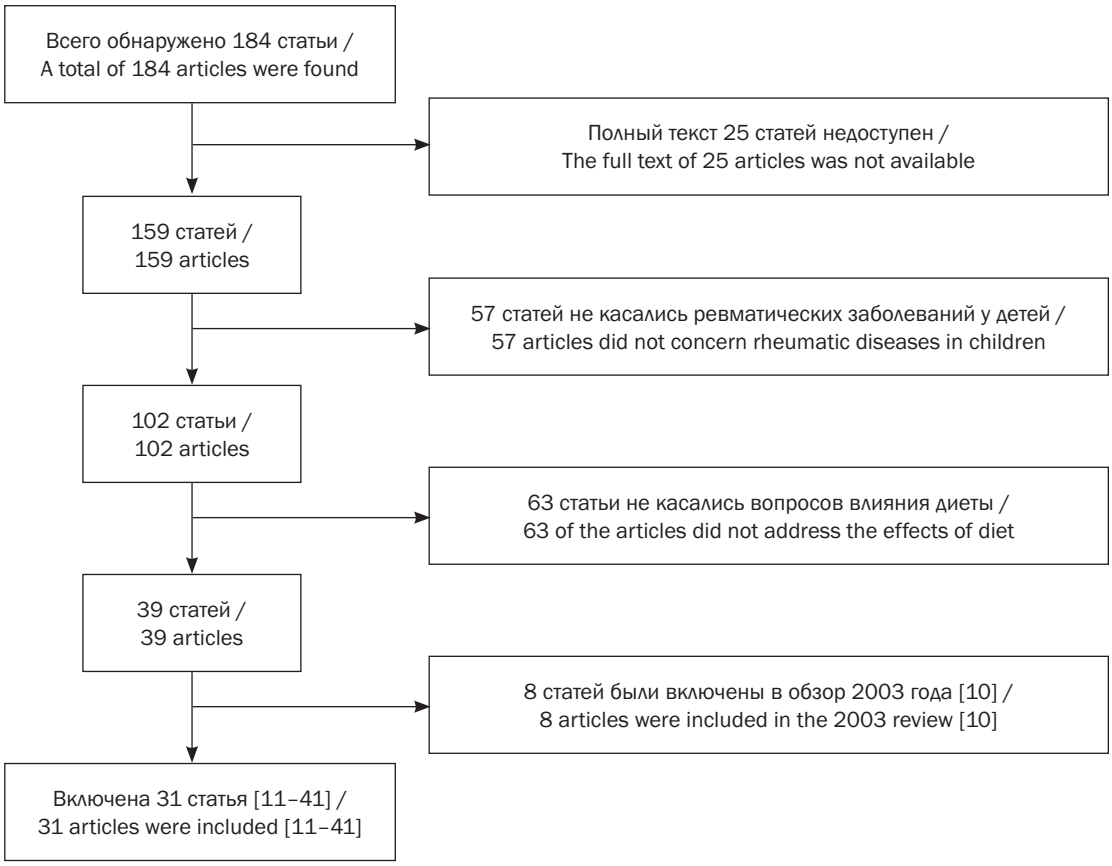

Fig. 1. Summary results of the conducted search, inclusion and exclusion of articles

Рис. 1. Суммарные результаты проведенного поиска, включения и исключения статей

JUVENILE IDIOPATHIC ARTHRITIS

Juvenile idiopathic arthritis is a heterogeneous group of chronic arthritis with onset before age 16 years, sometimes associated with extra-articular symptoms such as failure to thrive and gastrointestinal manifestations.

E.M. Little et al. in a 2019 study assessed the prevalence of the use of specific diets for JIA and the opinion of patients' parents about their effectiveness. An online survey was conducted for a year, in which about 20,000 people took part. Responses were received from 261 parents of patients with JIA. One third of patients (n=79) had experience with one or more specific diets, including gluten-free (66%), anti-inflammatory (41%), lactose-free (25%), vegetarian/vegan (20%). Of 79 parents of patients using the three most common diets, 50% reported reduced joint pain or swelling with the anti-inflammatory diet, 52% with gluten-free diet, and 65% with the lactose-free diet. However, the authors emphasize that prospective controlled studies are needed to test the effectiveness of a dietary approach to the treatment of JIA [11].

However, according to the 2021 American College of Rheumatology Guideline for the Treatment of Juvenile Idiopathic Arthritis, there is little evidence to support the use of any specific restrictive diet in the treatment of JIA. Unnecessary use of restrictive diets such as gluten-free and lactose-free diets may worsen nutritional status and increase the risk of other negative effects such as treatment delays, unnecessary costs and inconvenience. A healthy, balanced, age-appropriate diet is essential for maintaining health and quality of life in patients with JIA [12]. However, the use of an appropriate diet is certainly indicated in the presence of comorbid JIA with celiac disease or lactase deficiency.

Comorbidity of juvenile idiopathic arthritis with celiac disease and possible role of gluten-free diet in its treatment

S.M. Al-Mayouf et al. in a 2003 study investigated the prevalence of celiac disease in JIA and the correlation between serological markers and histological diagnosis of celiac disease. Serological markers of celiac disease (anti-gliadin IgA and IgG antibodies, anti-reticulin antibodies, and anti-endomysial antibodies) were tested in 42 patients (18 boys, 24 girls, aged 5 to 15 years). Endoscopic intestinal biopsy was performed in patients with positive serological markers of celiac disease. The diagnosis of celiac disease was based on classical detection of villous atrophy and crypt hypertrophy. In 18 patients (42.8%) suffering from various types of JIA (10 of them were diagnosed with systemic JIA, 5 with polyarticular and 3 with oligoarticular), various serological markers of celiac disease were identified, and in most patients, an increase in the level of several antibodies was detected. Anti-gliadin IgG antibodies were high in 14 patients (77.8%), 4 patients (22.2%) had high levels of anti-gliadin IgA antibodies, 7 patients (38.9%) had anti-endomysial antibodies, and 1 patient (5.5%) had anti-reticulin antibodies. Sixteen patients underwent intestinal biopsy, and only one patient with anti-endomysial antibodies (2.4%) had typical features of celiac disease on biopsy. After switching to a gluten-free diet, the patient with celiac disease showed improvement in both growth parameters and joint symptoms [13].

P. Sadeghi et al. in a 2021 study assessed the prevalence of celiac disease in 78 patients with JIA (mean age 7.9±3.9 years) who did not respond sufficiently to its standard treatment. In 3 patients (3.8%) with the oligoarticular JIA, the level of IgA antibodies to tissue transglutaminase was higher than normal. None of them had clinical symptoms of celiac disease. There were no significant statistical differences between the groups of seropositive and seronegative for antibodies to tissue transglutaminase patients with JIA in terms of growth disorders, gender distribution and different types of JIA. In one patient, a 10-year-old boy with a diagnosis of oligoarticular JIA with knee joint involvement established more than 2 years before inclusion in the study, celiac disease was confirmed by histological examination. He was recommended a gluten-free diet, after 2 months of which all clinical manifestations of musculoskeletal system completely disappeared. The dose of antirheumatic drugs was gradually reduced and then completely discontinued, and during 12 months of observation, the patient did not have relapses of arthritis against the background of adherence to a gluten-free diet [14].

Low-calorie ketogenic diet in juvenile idiopathic arthritis

The low-calorie ketogenic diet has been used for over a century to treat refractory epilepsy. It is currently gaining popularity as a potential therapy for obesity, as well as various chronic inflammatory diseases, including rheumatic diseases, since ketone bodies may have an anti-inflammatory effect. However, there have been no studies on the ketogenic diet in children with JIA to date. M. Rondanelli et al. in 2023 published a clinical follow-up of a 22-year-old woman with class I obesity and JIA, diagnosed at the age of 4 years. The patient followed a low-calorie ketogenic diet combined with a specially recommended physical activity program for 4 months, which resulted in a decrease in body weight from 78.3 to 72.8 kg, a decrease in body mass index (BMI) from 30.8 to 28.6 kg/m2. Her waist circumference reduces from 80 to 73 cm, body fat mass from 28.1 to 23.2 kg, free body fat mass from 45.7 to 41.9 kg, and visceral adipose tissue from 3.5 to 2.9 kg. In addition, the patient experienced a decrease in joint pain and an improvement in laboratory parameters of inflammation (reduction of C-reactive protein (CRP) level from 17 to 5 mg/L and in erythrocyte sedimentation rate (ESR) from 95 to 31 mm/h was observed) [15].

Specific carbohydrate diet in juvenile idiopathic arthritis

The specific carbohydrate diet is a nutritionally balanced diet that eliminates many complex

carbohydrates, such as grains, dairy products except for fermented milk products, starchy vegetables, and sugars except for monosaccharides found in honey. In addition, most processed foods are excluded, as they may contain emulsifiers and additives that have a negative effect on the intestinal mucosa. Thus, the diet includes meat, poultry, fish, eggs, nuts, fruits, beans, peas, honey, fermented milk products, and hard cheeses. Grains, rice, corn, potatoes, dairy products with a high lactose content, refined sugar and sweets are excluded on this diet. In 2021, L. Berntson published the results of a pilot study of possible anti-inflammatory effects of the specific carbohydrate diet in children with JIA, which had previously shown a good anti-inflammatory effect in children with inflammatory bowel diseases. The study included 22 patients with various types of JIA (age 6.3–17.3 years), with low to moderate disease activity, who had 2 or fewer inflamed joints and an ESR less than 30 mm/h. These patients had changes in concomitant therapy for at least 12 weeks before and during study inclusion. A study was conducted on 15 children who followed the diet for 4 weeks (of the remaining 7 patients, 6 withdrew from the study prematurely due to low motivation, in 4 cases on the part of the patients themselves, in 2 cases on the part of their parents, one family withdrew from the study due to an acute psychosocial situation). In the 15 patients who completed the study, the diet significantly reduced morning stiffness (p=0.003) and pain (p=0.048). Physical function, assessed by the Children's Health Questionnaire, also improved (p=0.022). Of the 15 patients who completed the study, 7 had active arthritis at enrollment, which was not detected in 5 of the 7 patients after 4 weeks of diet. However, in all 7 children with active arthritis at enrollment, multiplex analysis showed significant reductions in 9 inflammatory proteins, including tumor necrosis factor alpha (p=0.028), after 4 weeks of diet. Based on these results, the authors concluded that the specific carbohydrate diet may have a significant positive effect on the course of JIA, but further research is needed [16].

In 2023, Hagström et al. [17] conducted semi-structured interviews with 12 children and 15 parents (12 mothers and 3 fathers) from 13 families who had participated in the 2021 pilot study of the specific carbohydrate diet by Berntson [16]. Majority of those surveyed found participation in the study useful, with 12 of the 13 families reporting positive effects such as reduced joint pain and morning stiffness. Many participants reported that they would be willing to participate in a similar study again. It was not easy for children to deal with the social-emotional consequences of following the diet. Their parents faced practical problems because dieting required hard work, time, and money. Fields identified as requiring additional support included finding simple, quick and child-friendly solutions, strengthening organizational skills in nutrition such as meal planning and preparing for an intervention, relating to social and emotional aspects [17].

The role of gut microbiota and enteral nutrition in juvenile idiopathic arthritis

In recent years, the field of studying the role of microbiota in the pathogenesis of various chronic rheumatic diseases has been actively developing. M. Arvonen et al. published a literature review on the role of microbiota in JIA in 2020. In the section on diet therapy for JIA, the authors noted that patients often ask whether there is a place for a dietary approach in the treatment of JIA. The most honest answer that doctors can give is that there is probably a place for diet therapy in JIA, we just don't know what exactly it should consist of. The authors emphasize that at the time of writing the review, the only dietary approach for JIA for which there are published data is enteral nutrition based on mixtures containing everything necessary for adequate nutrition, with the complete exclusion of conventional foods from the diet. The authors cite data published by L. Berntson in 2014 and 2016, as well as those reported by him in personal communication. According to these data, a positive experience with enteral nutrition was initially recorded in one patient with

a polyarticular variant of JIA, refractory to treatment with methotrexate and several tumor necrosis factor alpha inhibitors. Then the patient was treated with two courses of enteral nutrition, both of which led to an improvement in functional indicators, the number of inflamed joints and morning stiffness. This was followed by a pilot study of enteral nutrition in 13 children with active JIA. Six of them refused therapeutic nutrition within 1–2 weeks, which indicates poor tolerance of this approach. Among the remaining 7, all who completed a 3–8-week course of enteral nutrition experienced a reduction in the number of inflamed joints and morning stiffness [18].

L. Berntson et al. in a 2022 study investigated whether the anti-inflammatory effect of two dietary approaches for JIA (enteral nutrition and a specific carbohydrate diet), demonstrated by them earlier, is associated with changes in the gut microbiome. The study included 16 patients with JIA (age 7–17 years), 6 of whom were treated with enteral nutrition and 10 with a specific carbohydrate diet for 4-5 weeks. Their clinical and laboratory status was assessed before and after treatment. Reduction of disease activity was statistically significant in both dietary approaches (p=0.03 for each). Gut microbiome test showed an effect of both interventions on its overall composition, with the most striking result being a decrease in relative abundance of Faecalibacterium in enteral nutrition and bifidobacteria with the specific carbohydrate diet. Gut microbiome alpha diversity was statistically significantly reduced in the specific carbohydrate diet (p=0.04) but not with enteral nutrition (p=0.22). Although the study groups were small, it was clearly shown that both enteral nutrition and specific carbohydrate diet influence the gut microbiome in JIA [19].

Nutritional status assessment in juvenile idiopathic arthritis

M.C. Caetano et al. in a 2009 study assessed the diet of 48 children and adolescents with JIA (19 boys, 29 girls aged 3 to 19 years, mean age 12 years) and compared it with the clinical and anthropometric characteristics of the patients, as well as with the drugs used in their treatment. Malnutrition was found in 8.3% of patients with JIA, and obesity was present in 16.7%. In patients with JIA, excess energy intake was noted in 12.5%, excessive protein intake — in 75% and excessive lipid intake — in 31.3% of cases. Low iron intake was found in 29.2%, low zinc intake — in 87.5%, low vitamin A intake — in 87.5% and low vitamin B_6 intake — in 64.6% of patients with JIA. However, no significant association was found between intake of energy, macro- and micronutrients, disease activity and nutritional status. Qualitative analysis of the diet showed low consumption of milk and its derivatives, fruits and vegetables and excessive consumption of oils and fats, as well as sugar and sweets [20].

M.M. Grönlund et al. in a 2014 study assessed the effect of JIA, its subtypes and disease activity on anthropometric measurements, body composition, and nutritional parameters in 40 patients with JIA (19 boys, 21 girls aged 3–10 years) compared with 40 healthy children matched for age and gender. Significantly higher values for central and peripheral adiposity were found in JIA patients compared with in healthy controls (mean waist circumference 55.9±4.9 vs. 53.4±3.7 cm, p <0.0001, and biceps skinfold thickness 6.2±2.3 vs. 5.3±1.7 cm, p=0.035, respectively) and obesity/overweight was more common (30% vs. 12.5%, respectively, p=0.056). Energy intake (kcal/day) was significantly higher in patients with JIA (p=0.036). Nutritional biomarkers such as hemoglobin, albumin, cholesterol and its fractions, triglycerides, 25-OH-vitamin D and serum folate levels were comparable in both groups. JIA subtype and disease activity did not influence body composition, energy intake or nutritional biomarkers. Thus, even patients with JIA with low disease activity have been shown to have more pronounced central and peripheral adiposity and consume more energy than their healthy peers [21].

A. Hari et al. in a 2015 study evaluated the relationship between macronutrient intake, body composition (lean body mass and fat mass) and bone mineral content in 33 patients with JIA (18 boys, 15 girls, mean age 10.4±4.3 years, median disease duration 2 (1–4.5) years). The median of lean body mass was 19 (13.8–

33.1) kg, fat mass — 5 (3.4–9.1) kg, and bone mineral content — 1044.9 (630.4–1808.9) g. The authors found a positive correlation between lean body mass and dietary intake of carbohydrate (r=0.4; p=0.03). No significant association was found between lean body mass and lipid or protein intake. No association was found between fat mass, bone mineral content and intake of carbohydrates, lipids and proteins [22].

D. Gorczyca et al. in a 2017 study assessed the association between dietary intake of ω-3 and ω-6 polyunsaturated fatty acids (PUFAs), their serum levels, and immune and inflammatory markers. The study involved 66 patients (16 boys, 50 girls aged 1.5 to 18 years, average age 8.6 years) with various types of JIA who were compared with a control group of 42 healthy children matched for age, gender, race, height, weight, and BMI. Dietary PUFA intake did not differ between the JIA and control groups. No relationship was found between intake of ω-3 and ω-6 PUFA and their serum levels. Total ω-6 PUFA and linoleic acid levels were higher in patients with inactive JIA than with active JIA. In patients with active and short-term disease (less than 3 months from diagnosis), arachidonic acid and docosahexaenoic acid levels were significantly lower than in the control group. Serum α-linolenic acid levels were significantly higher in patients with polyarticular JIA compared with patients with oligoarticular JIA and healthy peers. Negative relationship was established between serum ω-6 and ω-3 PUFA levels and the number of active joints, ESR, and CRP levels, and a positive relationship with the platelet count. The results of the study can identify a group of patients with JIA who may be recommended to take PUFAs in addition to their usual daily diet [23].

In late 2022 — early 2023, almost simultaneously, independently of each other, authors from Brazil [24], Greece [25] and the UK [26] published three reviews, including one systematic review and meta-analysis of studies on the relationship between nutritional status, dietary intake, symptoms and health-related quality of life in children and young people with JIA. It was shown that most of the studies indicate a suboptimal diet in children with JIA and the presence of a deficiency of a number of micronutrients that can be corrected with appropriate nutrition education conducted by experts. At the same time, some nutritional interventions, such as enteral nutrition and intake of ω-3 PUFAs may show some potential in terms of improving JIA symptoms. Thus, other dietary supplements, including vitamin D, as shown in a systematic review and meta-analysis by N. Zare et al. [26] are not associated with either improvement in JIA symptoms or improvement in the quality of life of patients.

The influence of parents' eating behavior

Parents' eating behavior, lifestyle, and food choices can directly affect their children's eating habits. L. Pereira et al. in a 2020 study assessed BMI, diet, physical activity, and lipid metabolite biomarkers in children and adolescents with various chronic rheumatic diseases, including the polyarticular JIA, and their parents, as well as the relationship between these parental indicators with those of their children. A total of 91 people were included in the study — parents and their children, 30 of whom (33%) were diagnosed with JIA. In total, 67% of parents and 27.5% of children were overweight (with JIA — 56.7 and 13.3%, respectively), in 80% of children with overweight, their parents also had it. The authors found a moderate association between total fat intake (Cramer's V test=0.254; p=0.037) and a weak association between intake of saturated fatty acids (Cramer's V test=0.219; p=0.050) and cholesterol intake (Cramer's V test=0.234; p=0.025) between parents and their children. High prevalence of dyslipidemia was observed in both parents (82.4%) and children (83.5%). A weak association was found between triglyceride levels in parents and their children (Cramer's V test=0.238; p=0.024), but no association was found between physical activity levels of parents and their children. High prevalence of overweight and dyslipidemia observed in parents, as well as the increased fat intake by parents and their children with chronic rheumatic diseases, indicate the importance of correcting the nutrition of these patients with the active involvement of their families in nutrition education programs [27].

The influence of maternal nutrition during pregnancy and child nutrition in the first year of life on the risks of developing juvenile idiopathic arthritis

E. Kindgren et al. in a 2019 study investigated the possible influence of maternal diet during pregnancy on the subsequent development of JIA. In a cohort of 15,740 newborns, the authors collected data on maternal diet, including fish consumption fish consumption, and obtained blood samples from mothers during pregnancy, as well as from their children at birth and at different ages. Sixteen years after the study began, JIA was diagnosed in 42 children, of whom 11 had antinuclear antibodies. Heavy metal analyses in cord blood were performed in all 42 patients who subsequently developed JIA and in 40 age- and gender-matched controls. It was found that maternal fish consumption more than once a week during pregnancy, as well as by the child himself during the first year of life, was associated with an increased risk of developing JIA ($p < 0.001$) and the presence of antinuclear antibodies ($p < 0.001$). Levels of aluminum (Al), cadmium (Cd), mercury (Hg), and lithium (Li) in cord blood were significantly higher in the group of children with JIA than in the control group. All children who were found to have antinuclear antibodies ate fish more than once a week during the first year of life. In patients with antinuclear antibodies, the levels of Al ($p < 0.001$), Cd ($p=0.003$), and Li ($p < 0.001$) in cord blood were significantly higher than in the control group. The frequency of maternal fish consumption during pregnancy correlated with the concentrations of Cd ($p=0.003$), Li ($p=0.015$), and Hg ($p=0.011$) in cord blood. Based on the results obtained, the authors conclude that moderate exposure to heavy metals associated with fish consumption during pregnancy and early childhood may affect the immune system, leading to the production of antinuclear antibodies and the development of JIA [28].

T. Hyötyläinen et al. in a 2024 study examined breast milk lipid composition in those mothers whose children later progressed to one or more immune-mediated diseases later in life, including 9 children with JIA, compared with breast milk lipid composition in mothers of healthy children. It was shown that maternal age, BMI, diet, and exposure to perfluorinated alkyl substances (PFASs) had a marked impact on breast milk lipid composition, with greater changes observed in the milk of those mothers whose children later developed autoimmune diseases. The authors observed features of breast milk lipid composition in mothers whose children later developed autoimmune diseases. However, due to the small number of study participants with each individual disease, they were all combined into one group, and differences in breast milk lipid composition in mothers of children with JIA compared to mothers of healthy children or children with other autoimmune diseases were not studied in this research [29].

JUVENILE SYSTEMIC LUPUS ERYTHEMATOSUS

Juvenile systemic lupus erythematosus (JSLE) is a chronic immune/inflammatory disease with various clinical manifestations depending on the affected organs or systems, which in children and adolescents, compared with adult patients, usually proceeds more severely. M.C. Caetano et al. in the 2009 study mentioned above in the section on JIA, also assessed the diet of 22 children and adolescents with JSLE (3 males, 19 females, aged 9 to 20 years, mean age 16.5 years) and compared it with the clinical and anthropometric characteristics of the patients, as well as with the drugs used in their treatment. Among patients with JSLE, 68.2% had a Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) >4. Malnutrition was found in 4.3% of patients with JIA, and obesity was present in 18.2%. In patients with JSLE, excess energy intake was noted in 13.6%, excessive protein intake — in 86.4%, and excessive lipid intake — in 36.4% of cases. Low iron intake was found in 50%, low zinc intake — in 86.4%, and low vitamin A intake — 95.2% of patients with JSLE. As in patients with JIA, no significant association was found between food intake, disease activity, and nutritional status in patients with JSLE included in this study [20].

S.G.L. da Silva et al. in 2018 published the results of a randomized controlled trial of the effect of nutritional intervention on lipid metabolite biomarkers associated with cardiovascular disease risk and their changes over time in patients with JSLE. The study included 31 adolescent girls aged 10 to 19 years who had been diagnosed with JSLE at least six months earlier. Patients were randomly assigned to the intervention group (15 patients, mean age 15.7±2.9 years) and the control group (16 patients, mean age 15.3±2.3 years). The mean disease duration, disease activity indices SLEDAI-2K and SLICC/ACR-DI did not differ significantly between the groups. Participants in the experimental group received oral and written nutrition guides once a month for 9 months. The intervention included the following steps: general orientation towards dietary behavior; ideas about healthy eating based on meal rotation; emphasis on adequate intake of carbohydrates and fats, including different types of fats, and attention to food labels; orientation towards adequate intake of salt, sugar, diet and light foods; qualitative changes in nutrition with an emphasis on fruits and vegetables (antioxidants), sea fish (ω-3) and intake of soluble and insoluble fiber; orientation towards diet and lifestyle, active leisure on weekends, and participation in parties and other events. After 9 months, the authors found a significant reduction in intake of calories (p=0.017), carbohydrates (p=0.030), total fat (p=0.020), saturated fat (p=0.013) and trans fat (p=0.012) in the study group compared with the control group. The activity of the high-density lipoprotein (HDL)-associated enzyme paraoxonase-1 by the end of the study was also significantly higher in the experimental group (p=0.021), indicating an improvement in HDL function and, as a result, a reduction in cardiovascular disease risks. In the control group, on the contrary, a significant increase in the level of low-density lipoproteins (HDL) was observed over time compared with the experimental group (p=0.018). The obtained data indicate that a rational diet in JSLE can help protect young patients from the premature atherosclerosis, the risks of which in JSLE are significantly higher than in the general population [30].

T.O. Abad et al., also in 2018, in the same group of 31 patients with JSLE, studied changes in body composition and assessed the association of total fat mass with clinical parameters. During the study period, the control group showed an increase in total fat mass by an average of 3.7 kg (p=0.013) and appendicular fat mass by 0.36 kg/m2 (p=0.007), while in the main group, no significant changes were observed in either total fat mass (p=0.446) or appendicular fat mass (p=0.494) over 9 months. Thus, 9-month diet therapy in patients with JSLE improved their eating habits and protected them from excessive body mass and fat deposits. However, the study did not reveal any association between total fat mass and physical activity, disease activity, or glucocorticoid use in either group [31].

In the 2020 study by L. Pereira et al., mentioned above in the section on JIA, the authors assessed the association between BMI, diet, physical activity, and lipid metabolite biomarkers in children and adolescents with various chronic rheumatic diseases, including JIAS, and their parents. Of the 91 patients included in the study, 41 (45%) were diagnosed with JIAS, 41.5% of whom were overweight, which was also observed in 65.9% of their parents. The data on the identified association between intake of total fat, saturated fat and cholesterol by parents and intake of these nutrients by their children are presented above in the section on JIA. However, it is worth noting separately that patients with JISC received a significantly higher dose of glucocorticoids than patients with JIA, and their use was associated with the presence of dyslipidemia (p=0.003), changes in the levels of LDL (p=0.017), HDL (p=0.043) and triglycerides (p=0.002) [27].

M.L.P Moreira et al. in 2021 evaluated fiber intake and its relationship with cardiovascular risk factors in 52 adolescents with JSLE (4 boys, 48 girls, mean age 16.7±1.5 years). The most common comorbidities identified were arterial hypertension (48%; n=25), dyslipidemia (44.2%; n=23), obesity (13.5%; n=7), and hyperglycemia (9.6%; n=5). Inadequate fiber consumption was observed in 61.5% of patients (n=32). Mean waist circumference (81.4 cm vs. 75.5 cm; p=0.02), waist-to-height ratio (0.51 vs. 0.47; p=0.02), and systolic blood pressure (122.1 mmHg vs. 114.8 mmHg; p=0.03) were higher in

those with low fibre intake. Among the assessed cardiovascular risk factors, waist-to-height ratio showed a significant negative correlation with fiber intake (r=–0.3; p=0.04). That is, the higher the fiber intake, the lower the waist-to-height ratio. Thus, low fiber intake in adolescents with JSLE is associated with higher levels of abdominal obesity and, consequently, with an increased risk of cardiovascular disease. Therefore, it is of utmost importance to assess and monitor the nutritional status of patients with JSLE and to develop strategies to promote adequate fiber and other nutrient intake [32].

JUVENILE DERMATOMYOSITIS

Juvenile dermatomyositis (JDM) is a rare autoimmune disease characterized by systemic inflammation, skin rashes and muscle inflammation, as well as loss of muscle mass, symmetrical weakness of proximal muscle groups, decreased physical performance and increased fatigue. M.Y. Solis et al. in 2016 published the results of a randomized placebo-controlled trial of the efficacy and safety of dietary supplements with creatine (methylguanidine-acetic acid is an amine compound found in food, especially in meat, and endogenously synthesized from amino acids, capable of improving functional indicators in healthy individuals, children with muscular dystrophy and adult patients with idiopathic inflammatory myopathies). Creatine was administered at a dose of 0.1 g/kg/day for 12 weeks to 15 patients with JDM (10 females, 5 males, aged 7–21 years) who had been on stable therapy for at least 8 weeks and were receiving no more than 40 mg prednisolone per day. Twelve weeks of creatine supplementation in patients with JDM were well tolerated and did not cause any adverse effects, but the treatment did not affect muscle function, muscle phosphocreatine content, or contribute to any other therapeutic effect. These data suggest that the beneficial effects of this supplement previously demonstrated in adults with idiopathic inflammatory myopathies are not replicated in patients with JDM, but may be related to the small number of participants in this study. Larger studies are needed to clarify the feasibility of creatine supplementation in children with JDM [33].

L. Pereira et al. in the 2020 study mentioned above in the sections on JIA and JSLE assessed BMI, diet, physical activity, and lipid metabolite biomarkers in parents of children and adolescents with JIA, JSLE, and JDM, and the relationship between these parental indicators and their children's indicators. A total of 91 people were included in the study — parents and their children, 20 of whom (22%) were diagnosed with JDM, 20% of whom were overweight, that was noted in 70% of their parents. The associations found between total fat intake, saturated fat intake, and cholesterol intake between parents and their children are presented above in the section on JIA, and the associations between glucocorticosteroid use (which were prescribed at the same frequency in JDM as in JSLE and, as in JSLE, were associated with the presence of dyslipidemia) and changes in LDL and HDL levels, as well as triglycerides levels are presented in the section on JSLE [27].

IGA VASCULITIS

IgA vasculitis is a systemic vasculitis that is most common in childhood and is characterized by non-thrombocytopenic purpura accompanied by joint pain and swelling, abdominal pain, hematuria and proteinuria. L.J. Xiong et al. in a 2019 randomized controlled trial studied the clinical effect of alanyl-glutamine-enriched nutritional support in the treatment of children with abdominal form of IgA vasculitis who required nutritional support. Patients were randomly divided into a control group receiving nutritional support without alanyl-glutamine (n=118) and a nutritional support group enriched with alanyl-glutamine (n=107). According to disease severity, intravenous glucocorticoids were used in both groups. Other treatments were the same in both groups. Two groups were compared in terms of the length of hospital stay, frequency and duration of intravenous glucocorticoid therapy, frequency of symptom recurrence during hospital stay, frequency of total parenteral nutrition, rate of weight loss, and frequency of fasting for more than 5 days. All patients were followed up for 3 months after discharge to monitor symptom recurrence. There were no

significant differences in the length of hospital stay, total parenteral nutrition, and frequency of fasting for more than 5 days between the two groups (p >0.05). Compared with the fortified nutritional support group, the control group showed a significant increase in the frequency and duration of intravenous glucocorticoid administration, symptom recurrence rate, and weight loss rate (p <0.05). After 3-month follow-up, all children returned to normal feeding, and the recurrence rate of abdominal symptoms in each group was less than 20%. The most common symptom was abdominal pain, followed by vomiting and bloating. No gastrointestinal bleeding was observed. All symptoms resolved after symptomatic treatment. No significant difference was found in the recurrence rate of abdominal symptoms between the two groups (p=0.693) [34].

L.H. Shang et al. in a 2021 study evaluated different enteral feeding regimens in children with abdominal form of IgA vasculitis who were hospitalized between August 2013 and August 2018. According to the starting time of enteral nutrition after abdominal pain relief, the children were divided into three groups: <24 hours (n=68), 24-48 hours (n=64), and 48–72 hours (n=60). According to the type of enteral nutrition, they were divided into another three groups: amino acid-based formula (n=53), extensively hydrolyzed lactoprotein formula (n=67), and normal diet (n=72). The recurrence rate of clinical symptoms and degree of satisfaction among family members were compared between groups. Based on the retrospective analysis, 166 children with abdominal form of IgA vasculitis were enrolled in a prospective study. All patients were given extensively hydrolyzed lactoprotein formula after abdominal pain relief. According to the feeding time after abdominal pain relief, they were divided into three groups: <24 hours (n=52), 24–48 hours (n=59), and 48–72 hours (n=55). The three groups were compared in terms of the recurrence rates of abdominal pain, rash, and hematochezia, the rate of use of parenteral nutrition and intravenous glucocorticoids, and the incidence rate of weight loss at discharge. The retrospective analysis showed that the children who were given extensively hydrolyzed lactoprotein formula for enteral nutrition at 24–48 hours after abdominal pain relief had a lower recurrence rate of clinical symptoms and the highest degree of satisfaction among their family members (p <0.0167). The prospective study showed that the children who were given extensively hydrolyzed lactoprotein formula for enteral nutrition at 24–48 hours after abdominal pain relief had lower recurrence rates of rash and abdominal pain, a lower rate of use of parenteral nutrition, and a lower incidence rate of weight loss at discharge (p <0.05). Thus, according to both retrospective and prospective studies, in children with abdominal IgA vasculitis, it is advisable and effective to start feeding with hydrolyzed milk formula based on lactoprotein 24–48 hours after the relief of abdominal pain [35].

D.H. Yin et al. in a 2021 study assessed the effect of animal protein in the diet on the risk of IgA vasculitis recurrence in 121 children who were hospitalized between October and December 2020. All children were assigned the same diet (animal proteins could be added to the diet 1 week after the onset of skin rash). Follow-up was performed at the outpatient service for half a year. According to the presence or absence of animal protein intake, the children were divided into an observation group (65 children) and a control group (56 children). The incidence of IgA vasculitis recurrence, times of skin rash recurrence and the incidence of kidney injury were compared between the two groups. According to the presence or absence of recurrence, the children were divided into a recurrence group (32 children) and a non-recurrence group (89 children). There was no significant difference between the observation and control groups in the incidence rate of IgA vasculitis recurrence, times of skin rash recurrence, and incidence rate of kidney injury (p >0.05). There was no significant difference in the daily intake of animal protein between the recurrence and non-recurrence groups (p >0.05). The multivariate logistic regression analysis showed that presence of kidney injury at initial onset, respiratory infection after treatment, and lack of exercise control were independent risk factors for the recurrence of IgA vasculitis in children (p <0.05). No significant association between animal protein intake and the recurrence of IgA vasculitis was found [36].

L. Wang et al. in a 2021 randomized controlled trial examined the effects of dietary guidance on the treatment of IgA vasculitis. Thirty children with IgA vasculitis (16 boys, 14 girls, mean age 6.9±0.5 years) followed a traditional restrictive diet for IgA vasculitis. They were prohibited from eating fish, shrimp, meat, eggs, milk, vegetables, fruits and spices, as well as raw, cold, hard and other stimulating foods. Three meals a day included rice, noodles, steamed bread, porridge and some salt. Patients were advised to drink warm boiled water. When the abdominal pain had disappeared and no new rash elements had appeared within 7 days, vegetables were added to the diet, usually in the following order: potatoes, cabbage, sweet potatoes, green vegetables, cauliflower, white cabbage, cucumber, etc. Also in this case, a small amount of fruit was added to the food in the following order: banana, apple, watermelon, pear, etc. The interval between adding two kinds of vegetables or fruits should be at least 5 days, and vegetables and fruits can be added in turn. After no new rash occurs in 1 month, a small amount of eggs and milk can be added. If the disease does not recur for 2 months after adding eggs and milk, a small amount of meat can be added to the diet. If skin rash, abdominal pain, and other recurring symptoms appear while expanding the diet, it is necessary to stop taking the added product and resume taking it after the situation stabilizes. Another 30 randomly selected children with IgA vasculitis (12 boys, 18 girls, mean age 6.95±0.47 years) formed a group of a dietary program. It was based on a conventional diet, which was adjusted through the results of the nutritional analysis, the recommended nutrient intake of children and the dietary norm, and the results of allergen monitoring. Children with cow's milk protein allergy were supplemented with amino acid-based formula, while children without allergy were supplemented with extensively hydrolyzed lactoprotein formula. Nutritional testing was conducted throughout the dietary adjustment process, including the addition of vegetables, fruits, eggs, milk, and meat. An additional 30 children with bronchitis, matched by gender and age (13 boys, 17 girls, mean age 6.9±0.6 years) and not suffering from food allergy or intolerance, were included in the comparison group. Children in the control group ate as usual without restrictions. No significant differences were found in the height, weight, and BMI of children in the three groups upon admission ($p > 0.05$). In addition, no significant differences were found in the indices of red blood cells, hemoglobin, serum albumin, serum prealbumin, calcium, and iron content in the three groups ($p > 0.05$). The study showed that the time of complete disappearance of skin rash in children in the experimental group was significantly shorter than in children in the group receiving a traditional restrictive diet (11.3±1.1 days versus 18.5±1.8 days, $p < 0.05$). Recurrent rash was observed in 6 children in the experimental group (20%), which was significantly less than in the group receiving a traditional restrictive diet (14 children (46.7%), $p < 0.05$). In the group of children receiving a traditional restrictive diet, kidney injury was observed in 19 children, including 13 children with isolated hematuria, and in 6 children hematuria was combined with proteinuria. In the group with the recommended diet, kidney injury was significantly less common — in 11 children from the group (8 children had isolated hematuria and 3 children had hematuria combined with proteinuria), 36.7% versus 63.3% ($p < 0.05$). In the traditional restrictive diet group, levels of nutrient intake and the actual/recommended percentage were lower, while the overall nutrient intake level of recommended diet group was higher and basically corresponded to the normal intake level. In addition, the actual intake and actual/recommended percentage of nutrients in the recommended diet group were significantly higher than those in the traditional restrictive diet group ($p < 0.05$). Thus, individual dietary recommendations may both improve nutrient and protein intake of children with IgA vasculitis and reduce the incidence the relapse of rash and renal complications [37].

KAWASAKI DISEASE

Kawasaki disease is an acute systemic vasculitis that most commonly affects children under 5 years of age. The disease is characterized by fever, bilateral conjunctival hyperemia, cervical lymphadenopathy, oropharyngeal mucosal changes, erythematous rash,

and erythema and edema of the distal extremities. It is the leading cause of acquired heart disease in children in most developed countries. Because Asian ethnicity is one of the main risk factors for Kawasaki disease, there are several theories of reasons for the differences in its ethnic prevalence. Theories suggesting genetic differences between populations are prevalent and are areas of active study by numerous research groups. At the same time, differences in diet between Eastern and Western populations are often presented as the cause of certain ethnic differences in the susceptibility to cardiovascular disease and cancer in adults. Surprisingly, dietary differences as a possible cause of the heterogeneous prevalence of Kawasaki disease among different ethnic groups had never been considered until 2013. At that time, M.A Portman first conjectured that the development of Kawasaki disease could be associated with increased soy consumption. This was based on studies that revealed the role of specific immune Fcγ receptors in the pathogenesis of Kawasaki disease and in its response to intravenous immunoglobulin therapy. The functions of Fcγ receptors are regulated by isoflavones contained in soy, in particular genistein, which are involved in the pathogenesis of Kawasaki disease by modulating the function of Fcγ receptors and disrupting the balance between activation and inhibition of inflammatory responses. Asian children consume significantly more isoflavones than Caucasian children of comparable age. Asian families usually add tofu to breastfeeding or formula feeding, starting at 4–6 months. This is exactly the age when Kawasaki disease begins to occur significantly more often than in children in the first six months of life. Moreover, infants fed tofu have higher concentrations of isoflavones in plasma and urine than adults consuming soy (who are almost never affected by Kawasaki disease) [38].

The hypothesis of M.A Portman et al. was confirmed in his subsequent 2016 study, which examined the dietary intake of soy and isoflavones immediately before the onset of the disease in a group of 181 children with Kawasaki disease (17% Asian, 61% boys, mean age 4.0 ± 3.7 years), compared with a control group of 193 healthy children (11% Asian, 51% boys, mean age 5.2±4.2 years). Surveys of mothers on soy consumption during pregnancy and breastfeeding revealed no significant differences between groups. More than half of the children in both groups did not receive soy, but mean isoflavone intake was more than twice as high in children with Kawasaki disease compared to the control group, especially among Asian children. The authors found a significantly increased risk of developing Kawasaki disease in children with total isoflavone (odds ratio (OR) 2.33; 95% confidence interval (CI) 1.37–3.96) and genistein (OR 2.46; 95% CI 1.46–4.16) intake compared with children who did not consume soy. A significantly increased risk of developing Kawasaki disease was observed in Asian children with the highest isoflavone intake (total isoflavones: OR 7.29; 95% CI 1.73–30.75; genistein: OR 8.33; 95% CI 1.92–36.24) compared with European children. Because Asian populations typically consume soy products in combination with other foods that are more common in their diets than in European populations, the authors further analyzed the association between noodle, white rice, and other grain consumption and Kawasaki disease. No relationships were found, supporting the hypothesis that Kawasaki disease is associated with soy products rather than with other foods commonly present in the Asian diet. Furthermore, dietary isoflavone intake in childhood, rather than maternal isoflavone intake during pregnancy and breastfeeding, is associated with the risk of developing Kawasaki disease in an ethnically diverse US population [39].

FAMILIAL MEDITERRANEAN FEVER

Familial Mediterranean fever (FMF) is the most common inherited autoinflammatory disease characterized by recurrent attacks of systemic inflammation lasting 1–3 days, manifested by fever, abdominal pain, joint pain, chest pain and skin rash. R.M.K. Ekinci et al. in a 2020 study assessed the impact of diet preference to the disease course in 74 children (30 boys, 44 girls, mean age 14.6±2.82 years) with FMF. A statistically significant (p=0.022)

higher rate of complete response to colchicine therapy was found in patients who preferred less salty and less fatty foods. Thus, it was shown that a low-salt and low-fat diet may be an additional option in the treatment of children with FMF. Further studies are needed to clarify the role of a low-salt and low-fat diet in the pathogenesis of FMF [40].

Y. Kazem et al. in a 2021 study examined the effects of anti-inflammatory diet on clinical manifestations and cognitive functions in 73 patients (39 males, 34 females, aged 7–24 years) with FMF. In addition to their usual doses of colchicine, patients followed an anti-inflammatory diet (rich in fresh vegetables and fruits, low in saturated and unsaturated fats and carbohydrates, low in food additives, sugar, fast food and semi-finished products) with additional curcumin intake (10 mg per day), flaxseed rich in omega-3 PUFA (2 teaspoons per day), and vitamin D (4000 IU per day) for 6 months. The results showed statistically significant improvements in clinical presentation in terms of duration, frequency and severity of attacks (p=0.05), subjective well-being (p=0.05), cognitive functions (p=0.05) and school performance (p=0.01). A decrease in CRP the levels (p=0.01) and an increase in the level of vitamin D (p=0.01), deficiency of which was observed in all patients at the time of inclusion in the study, were also noted. The potential of anti-inflammatory diet in terms of improving the clinical picture, cognitive functions and overall health of patients with FMF was shown. However, the authors recommend that the findings be confirmed by a randomized controlled trial [41].

CONCLUSION

The quality and quantity of studies investigating the role of diet in the development and treatment of rheumatic diseases in children remain insufficient. More research is needed before any specific diet can be widely recommended for children with JIA and other rheumatic diseases. Because the relationship between nutrition and rheumatic diseases is significant and bidirectional, dietitians should be knowledgeable about JIA and other rheumatic diseases and work closely with pediatric rheumatologists and other healthcare professionals. This is necessary to comprehensively improve the health of young patients and maintain their normal physical development despite the negative impact of chronic inflammatory disease and its aggressive treatment. In addition, pediatric rheumatologists would greatly benefit from having a dietitian on their team to promptly identify nutritional problems in patients and to suggest the best individual diet for each patient.

ADDITIONAL INFORMATION

The author read and approved the final version before publication.

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