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Review Article

Nutrition and Immunity: Implications in Inflammatory Processes Post Chikungunya

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Abstract

Although in other rheumatic conditions, role of nutrition, due to its importance for the immune system, has been largely explored, this is not the case of acute chikungunya or its chronic phase, the post-Chikungunya chronic inflammatory rheumatism (pCHIK-CIR). Given the relevant numbers and proportions of patients chronically affected in endemic and non-endemic areas (after returning with CHIK infection), a better understanding of the role of nutrition would be suitable, especially considering if the nutritional assessment and management, as found in this review, would be useful in the mitigation of the clinical consequences of pCHIK-CIR. This review explores these aspects.

Keywords: Chikungunya; Nutrition; Immunity; Chronic Disease; Infection

Abbreviations

AA: Arachidonic Acid; CHICK: Chikungunya; CHIKV: Chikungunya Virus; COX: Cyclooxygenase; NSAIDs: Non-Steroidal Anti-Inflammatory Drugs; pCHIK-CIR: post-Chikungunya Chronic Inflammatory Rheumatism; 5-LPOX: 5-lipoxygenase; FNkB: Nuclear Transcription Factor Kappa B; PUFAs: Polyunsaturated Fatty Acids; DHA: Docosahexaenoic Acid; EPA: Eicosapentaenoic Acid; PGE2: Prostaglandina E2; RA: Rheumatoid Arthritis; TOFA: 5-Tetradecyloxy-2-Furoic Acid; IgA: Immunoglobulin A; LDL: Low Density Lipoproteins; LTB4: Leukotriene B4; TNF-α: Tumor Necrosis Factor Alpha; IL1: Interleukin 1; IL-6: Interleukin 6; LTB5: Leukotriene B5; TXB2: Thromboxane B2.

Introduction and Development of the topic

Historically, there has been a very important association between nutritional deficiencies and infectious diseases, mainly associated with an inadequate modulation of the immune response, in that way, the risk of acquiring infectious processes by opportunistic microorganisms is directly proportional to person malnutrition degree [1-3]. The immune system is a specialized structure responsible to defense the individual against microorganisms (bacteria, viruses, and parasites), allergens, toxins, inflammatory cytokines and malignant cells. However, in conditions of malnutrition, either by default or by excess, associated with other factors such as stress or low physical activity, the immune system may be flimsy or suppressed [4]. Although that, little has been explored regard its importance in the context of acute or chronic chikungunya virus (CHIKV) infection, then the reason to explore this in the current review [4,5].

The post-CHIKV chronic inflammatory rheumatism (pCHIK-CIR) is a condition of clinical persistent disease after initial acute infection that is define when patients present, continuous or recurrently, joint pain, edema or rigidity, beyond 12 weeks post-infection [5]. As has been postulated and studied the immune and inflammatory response is particularly key in the origin and persistence of the pCHIK-CIR. Then, the question or hypothesis around the role nutrition, as factor that influence immune responses, is also valid in the context of pCHIK-CIR [6,7].

An adequate intake and absorption of nutrients in the body are necessary for the proper functioning of the defense systems, which participate from the synthesis of inflammatory markers of

acute phase that help to establish the diagnosis and severity of the process, until division and differentiation cellular of defense cells. However, we must considered that nutrients not only influence the responsible mechanisms for defending from pathogens, but also, in the prevention of pathologies such as anemia, pellagra, scurvy or coagulation disorders. At the immunological level, the nutritional requirements are necessary for: 1) The maintenance of immunological homeostasis or return to equilibrium after immunological responses; 2) bidirectional communication between the nervous and endocrine systems through neurotransmitters and hormones; 3) the phenomenon of tolerance towards one's own, thanks to which, the immune system does not react against the cells of the organism itself. An imbalance in any of these functions of the immune system can cause the expression of allergies, autoimmune diseases, and osteoarthritis, among others [9]. In other rheumatic diseases, as mentioned, this has been assessed, however, this raise the question of its importance in CHIKV, particularly at its chronic inflammatory rheumatism, which has been showed as significantly relevant in more than 50% of the patients infected with CHIKV [7,8].

Association between the immune system and gastrointestinal tract

The gastrointestinal system covers between 70-80% of all immunoglobulin-producing cells, which makes them the most important lymphatic system. Under normal conditions, the integrity of the intestinal wall has established by mucosal cells strongly linked by "tight junctions". Under normal conditions, disaccharides and peptides of more than two amino acids cannot cross the intestinal barrier, similar to what happens for antigenic molecules, which are absorbed through the epithelial layer by mechanisms of transcytosis; once inside the cell they are absorbed by the lysosomes that break them down into smaller molecules without antigenic capacity. If the structural or functional integrity of the epithelium has altered, molecules with antigenic capacity can cross it, reach the systemic circulation and trigger immune reactions [9-11].

The intestinal flora has great importance in the immunological modulation of the patients, in rheumatoid arthritis for example, the patients present intestinal inflammatory processes that are aggravated by the use of non-steroidal anti-inflammatory drugs (NSAIDs) and disease-modifying antirheumatic drugs, which predisposes to bacterial overgrowth in the small intestine. At a nutritional level, foods with many spices, cereal grains, lecithins (legumes/cereals), strong coffee, tea and alcohol can increase intestinal permeability and should therefore be consumed moderately [12]. In the opposite direction, the administration in enteral nutrition of prebiotics or fatty acids with anti-inflammatory activity, as well as the provision of important nutrients for the repair of mucosal lesions, such as short-chain fatty acids, glutamine or antioxidant vitamins, such as E and C [13].

Daily calorie and macronutrients requirements

A balanced diet with an adequate supply of energy is necessary for the proper functioning of the immune system [14,15]. On the other hand, hyper-caloric or hypo-caloric diets generate alterations in the responsiveness of the immune system [1,14]. Hyper-caloric diets have inflammatory hyper-reactivity, as opposed to low calorie diets, characterized by an increase in suppressor T cell activity with a decrease in circulating immune complexes with a decrease in the production of anti-DNA antibodies [15,16].

The nutritional and energy requirements have been estimated according to age, physical activity and physiological situation (pregnancy, basic illness, etc.). According to the basic principles of nutrition, a healthy diet is characterized by being sufficient, moderate, balanced, varied and innocuous. The diet should contain the maximum possible variety of foods, to guarantee an adequate supply of micro and macronutrients [17,18].

Anti-inflammatory activity of food

Fruits, vegetables, tubers, oils and oleaginous are the foods with the highest proportion of phytochemicals and main source of nutrients. The active phytochemicals in foods and the families of these have anti-inflammatory properties, these are: carotenoids, phenolic compounds, alkaloids, nitrogen compounds and organic sulfides [19].

Phenolic compounds are the most abundant group of bioactive substances present in foods with mainly dark and colorful pigments [20] in a wide variety of fruits, vegetables and spices, capable of interfering with biochemical and metabolic processes associated with the development and progression of inflammatory diseases, being able to inhibit mutagenic activity and activate detoxifying processes [21], antivirals and antioxidants. It is estimated that the daily intake of total phenolic acids from nature should not exceed 100 mg/day. However, colonic bacteria can transform anthocyanins, proanthocyanidins, flavanones, tannins and isoflavones, to phenolic metabolites, increasing their functional capacity [22].

According to Bellik and col. [19], phenols can be subdivided into phenolic acids, flavonoids, stilbenes, coumarins and tannins. Among these flavonodies is an important subfamily where flavonols, anthocyanidins, and is flavonoids are found.

Fruits and vegetables

Fruits and vegetables are essential components of a healthy diet and a sufficient daily consumption of them could contribute to the prevention of diseases, mainly those related to inflammatory processes. The consumption of varied fruits and vegetables guarantees most micronutrients such as dietary fiber [23], and a series of phytochemicals with antioxidant and anti-inflammatory effects that body need. Among these are: Grapes, wine, blackberries, bitter guava and pink flesh and skin, orange, grapefruit, lemon, mango, pineapple and avocados.

Vegetables

They are a large group of foods whose consumption is part of the global strategy that encourages the consumption of fruits and vegetables; they are the only natural sources of vitamins, minerals and fiber and have a low energy density. Considering the recommendations of consumption> 500g/d, several studies have been designed, demonstrating the efficacy of consumption in a number of variables, lipid profile, glucosidic, anthropometric [24], antioxidant and anti-inflammatory. Among these are: noni, onion, among others.

Tubercles

In general, it is established that there is a relationship between the concentration of the pigment in food and its phytochemical content. Fruits, vegetables, legumes and tubers, with a colored presentation, have procyanidins, anthocyanins and phycocyanins as well as other phytochemicals [25].

Blue fish

It has been suggested that the symptoms related to age improve with a diet enriched with active substances, vitamins and minerals. One of the fields of knowledge little explored is referred to the marine world, which represents an infinite reserve of bioactive ingredients, for its content of oils with omega-3, carotenoids, vitamins, minerals and peptides from sponges, algae and fish from waters deep, which provide a variety of health benefits. In this scheme, diet can represent a potential therapeutic agent. Thus, fish is a source of polyunsaturated fatty acids (PUFAs), carotenoids, phenolic compounds, galactans, alginates, substances that act as inhibitors COX1 and COX2, modulate the expression of nuclear transcription factor kappa B (FNkB) acting as potent anti-inflammatory, but from a regular intake [26]. Omega-3 fatty acids; Docosahexaenoic Acid (DHA), and Eicosapentaenoic Acid (EPA), have reached a singular importance, because they are able to inhibit a large number of steps in the cascade of inflammation from leukocyte chemotaxis, expression of molecules and interactions of the adhesion of leukocytes with the endothelium, production of eicosanoids up to the production of inflammatory cytokines and reactivity of helper T lymphocytes. In blue fish or dark meat fish and in fish oil, significant amounts of EPA and DHA have been found, establishing a dose-dependent effect [27].

Oils and oily

A group of foods that are used as additives in culinary preparations are oils and oleaginous, important for the type of fatty acids in their content. The oils of some seeds belong to this group and are important because of their composition in essential fatty acids such as linolenic acid (18: 3C), known as omega 3, which is converted to Eicosapentaenoic Acid (EPA) by desaturases and elongases (20: 5C) and later in Docosahexaenoic Acid (DHA) (22: 6C), its content reaches 55.3%, although its bioavailability from the diet is low, being necessary a regular consumption. Effects have been documented with the consumption of flaxseed in oil and extracts, being able to establish anti-inflammatory capacity, inhibiting the production of prostaglandina E2 (PGE2), leukotrienes, cyclooxygenase (COX) and Lipoxygenase (LOX) via the metabolism of arachidonate [28].

Spices

Peruvian food is recognized by the use of important amounts of condiments, which are used in small quantities as flavorings and colorants. These spices are phenolic compounds that are modulators of the anti-inflammatory response. The scientific information generated is broad, and the mechanism of action has to do with the fact that polyphenols can generate an anti-inflammatory effect on the basis of their antioxidant effect, modulating cellular signaling processes during inflammation. It has been found that it is precisely seasonings, spices and herbs that have an exceptionally high antioxidant power, mainly in dry products and a dose-dependent effect is established [29].

Effects of polyunsaturated fatty acids on the production of inflammatory cells

Essential fatty acids (n-3 and n-6) are important inflammatory precursors, known as eicosanoids, such as prostaglandins, leukotrienes and thromboxanes, all of which have pro- or anti-inflammatory properties [30,31]. Arachidonic acid (AA) is the most important substrate in the synthesis of certain eicosanoids considered proinflammatory, such as prostaglandins E2 and leukotrienes B4 [32]. Prostaglandins induce the production of proinflammatory cytokines in macrophages causing pain and vasodilation, while leukotrienes are chemotactic agents for leukocytes that cause local-

ized edema and ventilatory alterations [33]. Macrophages are part of the target cells in CHIKV infection during acute phase, but also important at the joint, where these infected cells migrate, particularly during chronic phase of disease [34]. However, eicosanoids are considered less inflammatory and even anti-inflammatory, if compared to the arachidonic acid derivatives, they also give rise to leukotrienes of series 5 (considered 10 to 100 times less potent), and prostaglandins of series 3 [33]. Arachidonic acid and eicosapentaenoic acid [EPA] are homologues that use similar metabolic pathways (cyclooxygenase [COX] and 5-lipoxygenase [5-LPOX]), however, EPA acts as a competitive inhibitor of AA [35], increasing its proportion in inflammatory cells compared to eicosanoids derived from AA [33]. The beneficial effects range from the decrease in the synthesis of inflammatory derivatives of arachidonic acid, to the synthesis of inflammatory suppressors such as resolvins [32,35,36]. Since decades ago was postulated that selective modulation of cellular arachidonic acid metabolism with thromboxane synthetase inhibitors temporarily reduced the yield of viruses hosted by human lung fibroblasts *in vitro*, including type I herpes simplex virus, vaccinia, vesicular stomatitis virus, Newcastle disease virus and CHIKV [37].

Therapeutic effects of polyunsaturated fatty acids in the inflammatory processes associated with rheumatoid arthritis

Numerous reports describe clinical benefits associated with n-3 fatty acids in patients with rheumatoid arthritis (RA), mainly in the reduction of pain severity, number of painful and/or swollen joints, and frequency of morning stiffness pain [30]. The effect of fatty acids has been documented in systematic [38,39] and non-systematic reviews [30,32,35,40-43] and contradicted by other authors [44,45]. Additionally, this effect depends on its source of procurance, in relation to the consumption of fish oil and rheumatoid arthritis, a study states that those patients who consume larger portions with or without olive oil obtain a significantly greater clinical improvement to those who don´t consume them [46,47]. However, the ideal dose has not been clearly established. In this sense, different studies suggest between 1-7 g/dl daily associated with a decrease in the intake of n-6 fatty acids [40,42,48-51]. Recently, some studies have found that Fatty acid synthesis is required for CHIKV replication [52]. On the basis of the demonstration of the antiviral activity of all lipid biosynthesis inhibitors targeting the proviral factors identified by the host genome-wide loss-of-function screen, the studies next considered all the other hits as putative drug targets. The cellular pathways in which human proviral genes are involved and identify druggable targets have been studied [52]. Twenty-one small-molecule inhibitors, some of which are FDA approved, targeting six proviral factors or pathways, have high antiviral activity *in vitro*, with low toxicity. Three identified inhibitors have prophylactic antiviral effects in mouse models of chikungunya infection. Two of them, the calmodulin inhibitor pimozide and the fatty acid synthesis inhibitor 5-tetradecyloxy-2-furoic acid (TOFA), have a therapeutic effect *in vivo* when combined. These results demonstrate the value of loss-of-function screening and pathway analysis for the rational identification of small molecules with therapeutic potential and pave the way for the development of new, host-directed, antiviral agents [52].

In relation to olive oil, it has been described as having anti-inflammatory and antioxidant properties [53-56]. The main active components of olive oil are oleic acid [belonging to the group of monounsaturated fatty acids], squalene and phenolic components [57]. Although the relationship between olive oil and RA has not been clearly established, the literature describes important therapeutic effects, such as the reduction of levels of inflammatory markers in blood and the inhibition of oxidative stress [57,58]. The phenolic fraction of olive oil is complex and heterogeneous, so it is proposed that its anti-inflammatory effect is due to its multiple components, or the interaction between them. Even so, the similarity between ibuprofen and olive oil has led to the discovery of a component that represents 10% of the phenolic fraction and has an important anti-inflammatory action, that is, oleocanthal [57].

In patients with rheumatoid arthritis and osteoarthritis, it is likely that oleocanthal exerts an anti-inflammatory action as a consequence of the inhibition of COX enzymes, however, it is necessary that the biological properties of each phenolic component be considered in the context of its absorption and interaction with others food components [54,57]. Experimental studies reveal that the administration of a diet constituted by olive oil is related to an increase in the production of IL-12 (cytokine with pro-inflammatory activity) and IL-4 (anti-inflammatory activity) [55,56]. In the case of IL-12, this cytokine is particularly important during acute, but also in chronic CHIKV [52].

Biological role of fiber

Ideal fiber inputs in the adult diet are around 20-35g/day or 10-14g for every 1,000 kcal. In general, the fiber consumed must have a proportion of 3/1 between insoluble and soluble. The main sources of insoluble fiber are wheat flour, bran or wheat germ, peas, whole grains, cabbage, root vegetables, cereals and ripe fruits. On the other hand, soluble fiber is acquired by the consumption of oats, plums, carrots, citrus, dried seeds and other legumes [59].

Pre and probiotics in inflammatory bowel disease

Another way to improve the probiotic bacteria´s profile is through the administration of prebiotics, substances that boost its growth. To consider a substance as a prebiotic: 1] shouldn´t be hydrolyzed, absorbed or digested in the stomach or in the small intestine; 2] should be a fermentable substrate by a group or groups of beneficial colonic bacteria, and stimulate their growth selectively; 3] should alter the colonic microflora, with predominance of lactobacillus and bifidobacteria, and induce luminal/systemic beneficial effects in the host [60]. This definition is overlapped with dietary fiber, except for selectivity by certain species. This selectivity has been shown for bifidobacteria, fructooligosaccharides, inulin, galacto-oligosaccharides and oligosaccharides [61]. Some types of fermentable fiber [such as the seeds of Plantago ovata], are precursors of short chain fatty acids, and could contribute to repair the intestinal mucus layer [62,63].

Probiotics

Supplement containing one or more cultures of intestinal flora which have beneficial effects for the host, by improving the endogenous flora [64,65]. Probiotics have been used in the prevention and treatment of diarrhea; The mechanisms of action involved include competitive inhibition for the adhesion of bacteria, synthesis of compounds that inhibit pathogens, stimulate intestinal response of Immunoglobulin A (IgA), decreased intestinal inflammation and hypersensitivity [64,66,67].

Prebiotics

Foods that promote the growth of probiotic bacteria, which have immunological effects, they have also been awarded an important role in lipid metabolism and regulation of minerals such as calcium and magnesium [65,68]. Non-digestible carbohydrates [oligo-and polysaccharides] are the most important candidates to be considered as prebiotics. These carbohydrates can be naturally present in foods such as milk and honey, as well as in vegetables, fruits, cereals, legumes and nuts. Prebiotics may also have a protective effect against intestinal infections. Several mechanisms have been described, one of which is based on the release, by many species of lactobacilli and bifidobacteria, of antimicrobial agents [short chain fatty acids and peptides] of broad spectrum of action [69]. Prebiotics also favor the absorption of minerals such as calcium, magnesium, zinc and iron due to the ability to join them, thus, preventing their absorption into the small bowel reaching the colon where they are released and subsequently absorbed [70].

Role of micronutrients in the immune system

Vitamins and minerals as a whole exert a relevant role in important metabolic pathways, being essential to conserve the structural and functional integrity of the immune system, in this way, fat-soluble vitamins [A, D and E], water solubility vitamins [Complex B and vitamin C] and some trace elements [iron, zinc, copper and selenium] exert important immune system modulator between proinflammatory and anti-inflammatory effects [71,72].

Malnutrition builds a syndrome composed of multiple types of nutritional deficiencies, which began to be described in animal nutrition sciences, who received diets lacking a single micronutrient, producing a characteristic symptomatology that would improve at the time of replacement [73].

Other important components of the diet may increase the risk of suffering a rheumatic pathology, such as coffee or tea, which seem to be associated with an increase in rheumatoid factor levels, mainly in women [74,75].

The Mediterranean diet is characterized by a high content of fruits, vegetables, legumes and unsaturated fats [especially olive oil], a moderate content of fish and a low content of dairy products and red meats [76]. These dietary changes [low concentrations of gluten and high levels of vitamin C and E] have atheroprotective, anti-inflammatory and antioxidant effects, thanks to the decrease in levels of Low density lipoproteins (LDL), IgA and free radicals [77,78], which is important in patients with rheumatoid arthritis where the immune system is altered [79], decreasing pain, morning stiffness, the number of inflamed joints, and improving physical function [80,81]. Then, this oriented diet would be of importance in patients with pCHIK-CIR, which tends to present such manifestations [6,34].

Materials and Methods

A retrospective and comparative descriptive bibliographic review study was carried out. In relation to the review, relevant to the topic immunity and nutrition, implications in inflammatory processes post chikungunya the researchers conducted a search of articles in the databases: Springer Link, Scielo, Dialnet, Lilacs, Pubmed and was supplemented with scientific literature not indexed in Google Scholar. Articles published from 1959 to 2017 were used. The search took place between November 2018 and January 2019 with the following descriptors: immunity, inflammatory processes, importance of nutrition. 105 articles were obtained, of them 13 articles were excluded, 8 were eliminated by the reading of the

title and finally 84 articles were considered as related to the subject of study.

Results and Discussion

Food is an important part of maintaining health not only because it provides the primary metabolites, minerals and vitamins necessary for the body's functions, but also because many of its secondary metabolites provide anti-inflammatory activity that could favor homeostasis by maintaining a balance between inflammation and anti-inflammation and in addition to serving as an adjunct in the treatment of inflammatory diseases such as non-communicable chronic diseases [82].

For Gonzales BM (2012), nutrition is a factor in the modulation of the inflammatory response. Photochemists present in food, in their original form or when metabolized, can form active metabolites and behave as intracellular messengers activating or inhibiting the expression of genes involved in inflammatory processes. One of the regimes that fulfills this characteristic is the Mediterranean diet, rich in vegetables, legumes, fresh and dried fruits, cereals, constant to low in saturated fats, with plenty of wine, olive oil and fish [20].

On the other hand according to Fauci AS and Langford CA (2007); the important thing is that with the adequate consumption of food it is possible to generate an anti-inflammatory environment by increasing the consumption of phytochemicals, controlling the intake of foods rich in PUFA-6, increasing the sources of PUFA-3, restricting foods that convert the AA into prostaglandins E2 and Leukotriene B4 (LTB4), and avoiding large intakes of carbohydrates that cause insulin spikes [83]. For Galarraga B and cols; all this is achieved by recommending a regular, continuous and daily intake of fruits and vegetables, to generate chemopreventive effects on health in the short and long term [31] and an adequate nutritional status.

Mesa MD, Galarraga B and cols, agree that essential fatty acids (n-3 and n-6) can act as precursors of chemical mediators of inflammation, known as eicosanoids, such as prostaglandins, leukotrienes and thromboxanes, all with pro- or anti-inflammatory properties. Depending on the precursor fatty acid, either the AA (derived from the n-6 fatty acids) or the EPA (derived from the n-3 fatty acids) and the cell where they are metabolized, eicosanoids of one or another series are synthesized [30,31].

For Hurst S and cols (2010); Inflammatory cells contain a high proportion of AA, this being the substrate mostly used for the synthesis of certain eicosanoids considered proinflammatory, such as prostaglandins E2 (PGE2) and leukotrienes B4 (LTB4) [40]. PGE2 induces the production of proinflammatory cytokines in macrophages causing pain and vasodilation whereas LTB4 is a potent chemotactic agent for leukocytes and activator of neutrophils giving rise to tumor necrosis factor alpha (TNF-α), to interleukin 1 (IL1) or to interleukin 6 (IL-6) by macrophages, however eicosanoids derived from EPA (n-3) are considered less inflammatory agents and even anti-inflammatory, when compared with those derived from AA. These eicosanoids give rise to leukotrienes of the series 5 (LTB5) (considered 10 to 100 times less potent as a chemotactic agent of neutrophils than LTB4), and to prostaglandins of the series 3 (PGE3). Given that AA and EPA are homologous and use the same metabolic pathways (cyclooxygenase (COX) and 5-lipoxygenase (5-LPOX)), EPA acts as a competitive inhibitor of AA, therefore, by increasing its proportion in the Inflammatory cells are consequently reduced to eicosanoids derived from AA (PGE2 and LTB4) according to Hurt S, Calder PC and cols, [32,33]. In this line, Hurst and Cols, conclude that the enzyme COX-2 is key in the inflammatory response and that the EPA is able to reduce the genetic expression of such enzyme, thus decreasing its activity (evaluated by the levels of PGE2 produced).

Caughey GE and cols (2010); In turn, they showed that suppression of COX activity by paracetamol improves with the intake of fish oil, so that those patients with higher plasma content of EPA have a greater degree of inhibition of the cytokines PGE2 and thromboxanes B2 (TXB2) at the plasma level compared to those patients with low EPA content [36]. These results coincide with those described by Calder PC, James M and cols (2008, 2010); where they described the importance of the synthesis of lipid suppressors of inflammation from n-3 fatty acids (resolvins) [32,35]. Likewise, Yacoubian S and cols (2007) stated that this line of research suggests that n-3 fatty acids, both EPA and docosahexaenoic acid (DHA), exert beneficial actions in humans through the biosynthesis of potent resolving mediators of inflammation [41]. Both EPA and DHA also cause significant inhibition of the receptors for tumor necrosis factor and inhibit the ability of AA to regulate these receptors, suggesting that this is the main effect of n-3 fatty acids on the inflammatory response according to Moghaddami N, [84]. In this line with the previously mentioned effects, we should highlight the clinical study by Remans, and cols, [44] in which they found a significant increase in plasma n-3 fatty acids (EPA and DHA) after supplementation with PUFA during four weeks, as well as a significant decrease in AA.

Several studies [45,48] of which two reviews and one clinical trial stand out, conclude that in order for a decrease in inflammatory mediators to occur, it must occur that the increase in n-3 fatty

acids is accompanied by a reduction in the intake of n-6 fatty acids. And, that a reduction in the intake of AA is the prerequisite to obtain an anti-inflammatory effect through the consumption of n-3 fatty acids. In this sense, the results of another study [40] has reminded that it is "important" that there is a balance in the consumption of both types of fatty acids, since an excess of any of them affects the other, reducing its incorporation into tissues and altering its biological effects due to the competition of both families of fatty acids for the same metabolic pathways.

Conclusion

Further studies are required in order to understand in more detail, the role of nutrition in immune mediation for the clinical evolution of pCHIK-CIR, particularly because nutritional assessment and intervention would help to mitigate the clinical consequences of this phase of the disease and also improve the quality of life, in addition to other therapeutic measures.

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