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Fish Oil and Inflammation: A Perspective on the Challenges of Evaluating Efficacy in *Trypanosoma cruzi* Infection

Maria Isabel Lovo-Martins, Marli Cardoso Martins-Pinge and Phileno Pinge-Filho

Abstract

Parasitic diseases constitute a big problem of ill health in both the tropics and subtropics as well as in more temperate climates and have been targeted by the Centers for Disease Control and Prevention (CDC) as priorities for public health in the USA. Parasitic infections can be caused by three types of organisms: protozoa, helminths and ectoparasites. They subsist on the host's nutrients at the host's expense. Effectively combating infections caused by parasites is essential for the survival of the organism. In this effort, cells and molecules of the immune system are susceptible to the modulating influence of fatty acids. The primary purpose of this chapter is to present a critical review of the multiple effects of fish-oil on *Trypanosoma infection*.

Keywords: *Trypanosoma cruzi*, Chagas disease, *n*-3 PUFAs, dietary fish oil, disease control

1. Introduction

Chagas disease, also known as American trypanosomiasis, is caused by infection with the hemoflagellate protozoa *Trypanosoma cruzi*. This disease was first described in 1909, by the epidemiologist Carlos Justiniano Chagas. In this pioneering work, not only the etiological agent *Trypanosoma cruzi* was described, but also its evolutionary forms, life cycle, epidemiology and clinical manifestations of the disease was fully reported [1]. More than a century after this discovery, it is estimated that Chagas disease still affects around 6–7 million people worldwide, especially in Latin America, with more than 10,000 deaths annually [2]. Currently, Chagas Disease is considered as a neglected tropical disease by the World Health Organization [3].

The progression of Chagas disease is characterized by the occurrence of three phases: acute, indeterminate and chronic. Survival during the acute phase of infection requires an inflammatory response involving cells of innate immunity, such as macrophages, dendritic cells and natural killers whereas in the chronic phase the T-lymphocyte-mediated immunity maintains parasite replication under control [4]. However, evidence suggests that the exacerbated inflammatory response of the host is one of the most determinant factors in the progression of Chagas disease, along with the virulence and tropism of the strain [5, 6].

During *T. cruzi* infection—as in other infections—the immune system acts to protect the host from infectious agents and the nutrient status is an important factor contributing to immune response [7]. Between the components from the diet, fatty acids found in oils and oily food have an important role not only in the structure of cell membranes, energy source or as hormones precursors [8], but acts directly as modulators of the immune response [9]. Specifically, the consumption of fatty acids from the family of omega-3 polyunsaturated fatty acids (*n*-3 PUFAs), found in large amounts in fish oil, has been associated with anti-inflammatory and immunomodulatory effects [10]. Taking this into account, an important issue to be raised is the effect of *n*-3 PUFAs supplementation on infectious diseases, such as Chagas disease, where an efficient—but controlled inflammation—is necessary and important for host defense [11].

Currently, daily oral supplementation with *n*-3 PUFAs is recommended by the American College of Cardiology and American Heart Association as an important adjuvant in the treatment of heart failure [12]. In the same sense, daily oral supplementation with *n*-3 PUFAs is recommended by the Brazilian Directive on Dyslipidemias and Prevention of Atherosclerosis, updated in 2017 by the Brazilian Society of Cardiology (2–4 g daily), as an important complement in the prevention of atherosclerosis and its cardioprotective benefits [13]. Despite the recognized relevance of *n*-3 PUFA supplementation in the supplementary treatment of cardiovascular diseases, and considering the important cardiac compromises that may occur during the chronic phase of Chagas disease, supplementation with *n*-3 PUFAs may in fact represent a perspective for the additional treatment of patients affected by Chagas disease. However, the immunomodulatory effects of the dietary supplementation with *n*-3 PUFAs and the relationship with the host response and resistance to *T. cruzi* infection should be carefully considered.

2. Polyunsaturated fatty acids

Polyunsaturated fatty acids (PUFAs) are a class of fatty acids with 18–22 carbons (C18–C22) containing two or more double bonds in the carbon chain. The most important PUFAs for human health and nutrition are the omega-6 (*n*-6) and omega-3 (*n*-3) families. The classification of the fatty acids between this families is made considering the position of the first double bond counting from the methyl end of the fatty acid chain [14]. Linoleic acid (LA) is considered the parent fatty acid of the *n*–6 PUFAs family, while α-linolenic acid (ALA) is considered the parent fatty acid of the *n*–3 PUFAs family. Both LA and ALA cannot be made by humans or other mammals, thus they are considered essential fatty acids and have to be supplied in the diet [15].

The *n*-6 PUFA LA (18:2n-6) could be found naturally the seeds of most plants except for cocoa, coconut, and palm. On its turn, the *n*-3 PUFA ALA (18:3n-3) is found in the seeds of flax, rape, chia, perilla, walnuts (and their vegetable oils) or even chloroplast of green leafy vegetables. In the body, both LA and ALA are metabolized to longer-chain fatty acids of 20 or 22 carbons [15, 16]. LA is metabolized to arachidonic acid (AA), a long chain *n*-6 PUFA (LC *n*-6 PUFA) whereas ALA is metabolized to eicosapentaenoic acid (EPA, 20:5n-3) and docosahexaenoic acid (DHA, 22:6n-3), a long chain *n*-3 PUFAs (LC *n*-3 PUFA). This reaction occurs through the actions of elongases enzymes, that increase the chain length; and desaturases enzymes, which add extra double bonds to the carboxyl end of the fatty acid, increasing the degree of unsaturation [17]. Humans and others mammalians could convert LA in AA; and ALA in EPA and DHA, however this process is slow.

Although there is a competition between *n*-6 PUFAs and *n*-3 PUFAs for the desaturation enzymes, which prefer the ALA instead the LA, the Western diet provides higher amounts of LA than ALA, being the AA the main unsaturated long-chain fatty acid produced [18]. Therefore, the most efficient way to increase the amount of LC *n*-3 PUFAs in the body is through directly ingestion of primary sources EPA and DHA, as the seafood. The LC *n*-3 PUFAs are found in high amounts in most seafood, especially in oily fish, in the blubber and tissues of sea mammals like seals and whales or even in supplements like fish oils, cod liver oil, krill oil, algal oils and in pharmaceutical grade preparations [10].

3. Immunomodulatory effects of long chain *n*-3 polyunsaturated fatty acids

Experimental assays have shown that diet supplementation with LC *n*-3 PUFAs results in powerful anti-inflammatory and immunomodulatory activities in a range of diseases, such as autoimmune [19], inflammatory bowel disease [20], rheumatoid arthritis [21] and even infectious diseases [22–25]. There are also clinical trials in human patients associating the use of supplements rich in LC *n*-3 PUFAs with the evolution of inflammatory diseases [26] and infections, such as sepsis [27]. Studies in patients with rheumatoid arthritis are those that present better results, with several tests showing reduction of symptoms, such as morning swelling, pain and stiffness [28].

Inflammation is a fundamental component of the body response to infections or injuries that involves the interactions among many different cell types. The leucocytes are cells from immune system found in the peripheral blood and lymph tissue that actively participate in the inflammation, being specially involved in body defense and protection [29]. Typically, inflammation is transient, exerting a protective role in the body. However, when the inflammation does not end and the acute response become chronic, this uncontrolled response leads to more injury [29]. Therefore, inflammation is the pathological mechanism behind many chronic diseases, and that is why the immunomodulatory effects of LC *n*-3 PUFAs are considered to be potentially beneficial.

Some mechanisms of the immune response modulation by LC *n*-3 PUFAs are already known, such as modification of function and composition of immune system cell membranes, change in the pattern of eicosanoids produced and in the cytokine profile, regulation of gene expression and proliferation of T lymphocytes [30]. The leukocyte membrane phospholipids from humans consuming a Western diet typically have 15–20% of AA, 0.5–1% of EPA and 2–3% of DHA. When fish oil rich in LC *n*-3 PUFAs are incorporated to the diet, increased amounts of EPA and DHA are incorporated in these phospholipids in a time and dose dependent fashion, and it is occurs at the expense of AA [31, 32]. These changes in membrane fatty acid composition subsequently modify the cell-membrane fluidity, production of eicosanoids and the formation of lipid rafts [17, 33].

4. Long chain *n-3* PUFAs and *Trypanosoma cruzi* infection

Infection with *T. cruzi* causes a strong inflammatory reaction at the inoculation site and, later, in the myocardium [34]. Approximately one-third to one-half of patients with indeterminate disease will eventually develop chronic Chagas cardio-myopathy (CCC). CCC results from the combined effects of persistent parasitism, parasite-driven tissue inflammation, micro-vascular and neurogenic dysfunction, and autoimmune responses triggered by the *T. cruzi*-infection [34, 35].

There are few studies on the effects of increased consumption of LC *n*-3 PUFAs rich foods as well as the long-term effects of LC *n*-3 PUFAs on inflammatory profile and clinical outcomes in CCC. Recently, a group of Brazilian researchers reported that patients aging >18 years, with a diagnosis of CCC, that received LC *n*-3 PUFAs capsules (1.8 g EPA and 1.2 g DHA) during an 8-week period, presented modifications in the lipid and inflammatory profile, demonstrated by a decrease in triglycerides and improvements on IL-10 concentration [36]. The same group had already supposed in 2013 that the anti-inflammatory action of LC *n*-3 PUFAs may have beneficial effects on chronic chagasic cardiomyopathy, and could be translate into a less severe progression of cardiomyopathy, with subsequent reduction in morbidity [37].

In mice, the resistance to acute infection has been shown to be dependent on interferon IFN-γ that activates macrophages to produce nitric oxide (NO) and kill the obligate intracellular amastigote form of the parasite [38–40]. In addition, TNF-α provides a second signal stimulating NO production and anti-*T. cruzi* activity in IFN-γ-activated macrophages.

TNF-α is a cytokine that appears rapidly after infections or lesions, playing a key role in fighting invasive pathogens. However, excessive TNF-α production is related to mortality and morbidity in sepsis [41], meningitis [42] and malaria [43]. Although many of the studies about TNF-α modulation by treatment with LC *n*-3 PUFAs indicate a suppressive effect on this cytokine production, there are studies reporting an increase in cytokines production by treatment with LC n-3 PUFAs. Increased TNF-α production was reported by macrophages stimulated in vitro with LPS [25]. Dietary supplementation with fish oil on experimental *Klebsiella pneumoniae* infection and in brain-infection by *Plasmodium berghei* led to increased *ex vivo* production of TNF-α and IL-1α by *in vitro* LPS-stimulated macrophages [24]. Also, the *in vivo* treatment with fish oil increased TNF-α plasma levels in mice infected with *Listeria monocytogenes* in the first 24 hours of infection, being lower in later times [44]. In addition, specifically in *T. cruzi* infected-mice that were supplemented with fish oil rich in LC *n*-3 PUFAs it was related increased TNF-α production by the spleen cells [22].

The first work on the in vivo effects of PUFAs supplementation on *T. cruzi* infection was published in 1958 by Godfrey and coworkers. They showed that oral supplementation with cod liver oil, rich in LC *n*-3 PUFA, associated with vitamins A and D, suppressed mice infections with *T. congolense* and *T. vivax*, but showed no effect on mice infected with *T. cruzi* or *T. brucei* [45]. However, when vitamin E was used together with cod liver oil, these adverse effects on host resistance on *T. congolense* and *T. vivax* infection were reversed, suggesting that diet-induced oxidative stress and vitamin E deficiency were central to this particular diet-infection relationship.

In 1995, Takeda and collaborators reported that daily oral administration of the LC *n*-3 PUFA EPA, present in great amounts in fish oil, greatly diminished host survival following an experimental infection with *T. cruzi* [46]. As in the work of 1958, they included vitamin E in EPA treatment, in order to try to avoid the oxidative stress problem. The authors reported that their EPA-treatment failed to impact tissue parasitism, but was associated with elevated capacity to produce the inflammatory cytokine TNF-α.

In contrast, more recently our research group has described that oral supplementation with fish oil on *T. cruzi* infected-mice did not change the mortality rate, but it did alter the course of parasitemia, as well as other important host responses, such the increased TNF-α production [22]. In *T. cruzi* infected-mice that were supplemented with fish oil rich in LC *n*-3 PUFAs we observed a transient, but substantial, increase in peak circulating parasitic load at the 7th day post infection. At the 12th day post infection, these fish oil-treated mice had similar

levels of parasitemia in the blood compared to controls groups (mice treated with saline or corn oil). Surprisingly, besides de high peak of parasitemia, the mice that were treated with fish oil rich in LC *n*-3 PUFAs showed significantly fewer parasites in their cardiac tissue at the 12th day post infection (**Figure 1**) compared to mice treated with saline or corn oil. The oral supplementation with corn oil was used an alternative fat source rich in the *n*-6 PUFA linoleic acid but poor in LC *n*-3 PUFAs [22].
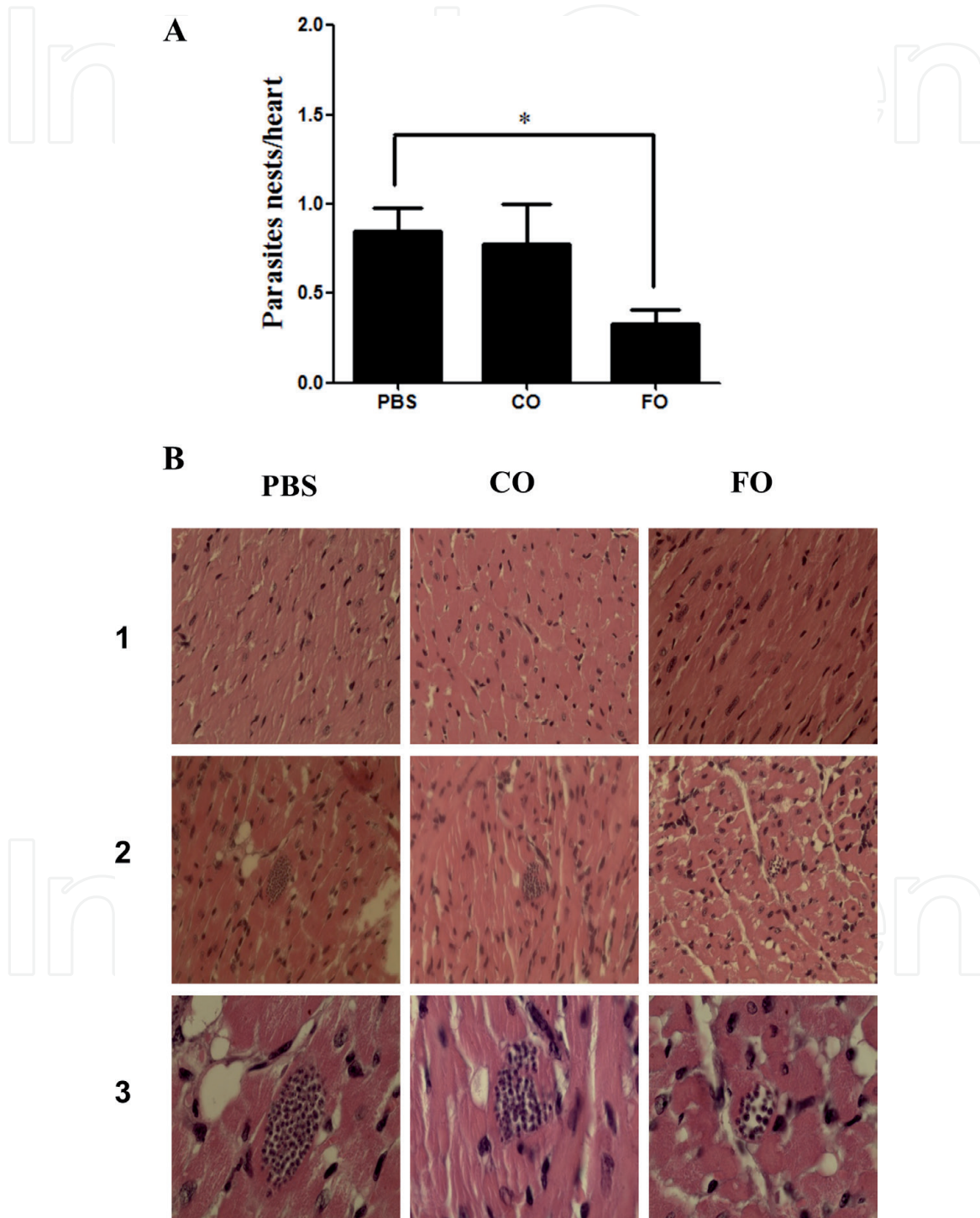
Figure 1.
Effects of FO supplementation on cardiac parasitism. From 15 days before T. cruzi infection until the 12th day post infection, C57BL/6 mice were supplemented by gavage with 0.6% (v/w) saline, corn oil, or menhaden fish oil. C57BL/6 mice were infected with 5 × 10³ blood trypomastigotes T. cruzi (Y strain). Cardiac parasitism (A): three heart sections were counted for each animal, and the results are expressed as means ± SEM of three sections from five animals per group and are representative of two independent experiments. Cardiac tissues (B) were examined by hematoxylin and eosin staining from uninfected mice (1) on day 12 after T. cruzi infection (2 and 3). Original magnifications were 400× (1 and 2) and 1000× (3). Original publication [22].

In humans, as in some experimental animals, *T. cruzi* infection is associated with anemia, thrombocytopenia, leukopenia and bone marrow hypoplasia [47–50]. Dietary supplementation with fish oil had no effect on the anemia of *T. cruzi*-infected mice [22], a finding that contrasts with the improvement in malaria-induced anemia reported by the treatment with LC *n*-3 PUFAs [46]. However, thrombocytopenia and leukopenia were less severe in *T. cruzi*-infected mice orally treated with fish oil [22].

The production of eicosanoids represents an important role in the regulation between the host's immune response and the establishment of *T. cruzi* infection (**Figure 2A**). Eicosanoids are lipid mediators of inflammation which include prostaglandins (PG), thromboxanes (TX), leukotrienes (LT) and lipoxins (LX). The initial substrate for the synthesis of eicosanoids is the lipids present in the membrane phospholipids of cells involved with inflammatory processes. In individuals with a regular western diet, AA is the most prevalent fatty acid in the inflammatory cell membrane, and it is usually the main substrate for the synthesis of eicosanoids, giving rise to series 2-series prostaglandins and thromboxanes and 4-series leukotrienes and lipoxins [30].

Acute *T. cruzi* infection in murine models is characterized by cardiac lesions associated by high levels of PGE_2 [51]. During acute *T. cruzi* infection, both PGE_2 and its EP_2 receptor are involved in inflammation and cardiac inflammatory infiltrate [52], as leukotrienes, that is important for the local production of NO and cardiac parasitism control [53, 54]. Additionally, plasma PGE_2, TBX_2 e 6-oxo-$PGF_{1\alpha}$ levels are increased in murine models of acute infection [55, 56]. In addition to cardiac effects, PG are associated with immunosuppression of infected animals, with reduction in lymphocyte proliferation, on TNF-α levels, and in the microbicidal functions of macrophages [57, 58].

In vitro assays have shown that the phagocytosis of apoptotic cells by macrophages during *T. cruzi* infection potentiates the release of PGE_2 and transforming growth factor-beta (TGF-β) by these cells. These macrophages become refractory to inflammatory cytokines, consequently decreasing NO production and allowing parasite survival and growth even in an immune response environment [59]. Also, the pharmacological inhibition of the COX enzyme with aspirin in macrophages decreased the trypomastigotes internalization in these cells, with increase of interleukin-1 (IL1-β), NO and lipoxins [60]. In addition, PGE_2 elicits signaling pathways capable of instantaneously inhibiting NLRP3 inflammation activation [61]. This may be relevant in the context of *T. cruzi* infection, since the activation of the inflammatory complex NLPR3 and caspase-1 is important for parasite control during the acute phase of infection, leading to activation of trypanocidal activities in macrophages, as NO production [62].

Although PGE_2 is important for the parasite survival at the beginning of infection, the *in vivo* pharmacological blockade of COX enzymes during the acute phase of *T. cruzi* infection leads to higher levels of parasitemia, lower survival rates of experimental mice and increased cardiac parasitism [63–65]. However, COX blockade with aspirin already in the chronic phase (60 days after infection) does not cause an increase in parasitemia or mortality, but is associated with an improvement in the cardiac ejection fraction [64].

Confirming the relevance of inflammatory-lipid mediators during *T. cruzi* infection is the fact that the parasite itself synthesizes prostaglandins and thromboxanes (TX) [66]. Infective stages of *T. cruzi* have the enzyme phospholipase A-1, important for the release of fatty acids (such as AA) from the membranes and for eicosanoid synthesis, as represented in **Figure 2A**. From AA, *T. cruzi* preferentially
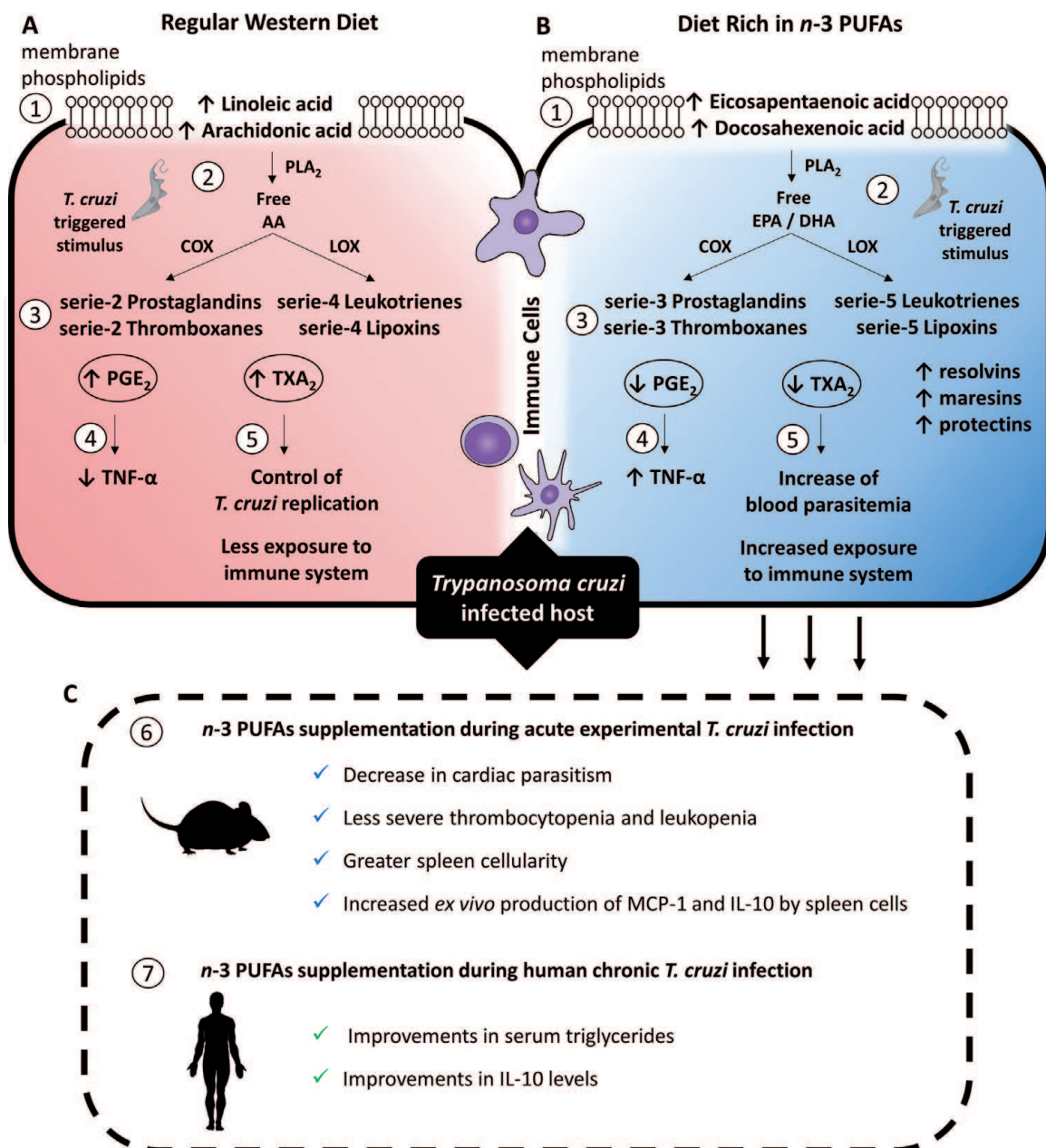
Figure 2.
Mechanism and effects of PUFAs n-3 PUFAs supplementation on Trypanosoma cruzi infection. **1**—*The traditional western diet provides to immune cells great amounts of n-6 PUFAs arachidonic acid and linoleic acid, while a diet supplementation with LC n-3 PUFAs results in eicosapentaenoic acid and docosahexaenoic acid incorporation into immune cells plasma membrane phospholipids [31, 32].* **2**—*T. cruzi infection trigger inflammatory stimulus, as the expression of cyclooxygenase (COX) and Lipoxygenase (LOX) enzymes [53, 55]. The enzyme phospholipase A² (PLA²) removes fatty acids from the membrane phospholipids, mainly arachidonic acid (AA) in cells from western diet and mainly eicosapentaenoic acid (EPA) or docosahexaenoic acid (DHA) from n-3 diet.* **3**—*The enzymes COX and LOX uses the free fatty acids for eicosanoids synthesis. When AA is used as substrate 2-series prostaglandins/thromboxanes and 4-series leukotrienes/lipoxins are formed. When the substrate is EPA or DHA, a switch in the class of eicosanoids produced occurs, being produced 3-series prostaglandins/thromboxanes and 5-series leukotrienes/lipoxins [30], as well mediators that act in the resolution of inflammation: E-series resolvins generated from EPA, D-series resolvins from DHA, and protectins and maresins from DHA [72, 73].* **4**—*In the acute phase of infection, the high production of prostaglandin E² (PGE²) leads to a transient immunosuppression, with decreased TNF-α production by the host [57]. The immune cells from n-3 diet produce lower amounts of PGE₂, and consequently more TNF-α [22].* **5**—*The thromboxane A² (TXA²) produced during T. cruzi infection is associated with a control mechanism of parasite proliferation and less exposure to immune system [67]. The decreased TXA² production that occurs in cells from n-3 PUFAs diet could explain the increased parasitemia that were previously observed in vivo, leading to more T. cruzi exposition to immune system [22].* **6**—*Effects of in vivo supplementation of experimental mice during acute T. cruzi infection [22].* **7**—*Effects of in vivo supplementation of human patients with chronic Chagas cardiomyopathy [37]. Original publication [22].*

synthesizes TXA_2, in addition to small amounts of $PGE_{2\alpha}$ [67]. During acute infection, TXA_2 produced by the parasite acts on the vascular endothelium creating an inflammatory phenotype, increasing the expression of adhesion molecules and directly participating in the parasitemia control and host survival. The absence of TXA_2 receptor in infected-host cells leads to large cellular parasitism, when compared to cells that have the receptor. This indicates that *T. cruzi* has a self-regulated mechanism that controls its proliferation trough TXA_2 [67]. The effects of both TXA_2 produced by the parasite and the PGE_2 produced by the host create an immunomodulatory environment that favors the survival of the host, an indispensable factor for the survival of the parasite and maintenance of the chronic phase of the infection [63, 67].

When incorporated into cell plasma membrane, LC *n*-3 PUFAs competitively inhibit the formation of eicosanoids from AA by the enzymes cyclooxygenase (COX) and lipoxygenase (LOX), being produced, from the fatty acids EPA and DHA, 3-series prostaglandins and thromboxanes and 5-series leukotrienes and lipoxins. These eicosanoids produced from the EPA and DHA have less inflammatory activity [68, 69]. This effect occurs in part due to the reduction of AA available, but also due to a direct action of the EPA decreasing the activity and expression of the COX-2 enzyme, that is responsible for the synthesis of prostaglandins after an inflammatory stimulus [70].

We have shown that fish oil supplementation decreased the production of PGE_2 in mice uninfected (**Figure 3A**) and infected with *T. cruzi* (**Figure 3B**) [22], as also represented in **Figure 2B**. In addition, as discussed above, it is reported in the scientific literature that LC *n*-3 PUFA supplementation promotes the production of 3-series thromboxanes, rather than the production of 2-series thromboxanes, a lipid mediator described as important for the regulation and continuity of infection by *T. cruzi* [67]. The use of LC *n*-3 PUFAs to modulate the production of eicosanoids exhibit relevant differences when compared to the use of pharmacological inhibitors of COX isoforms. While pharmacological COX blockade results in a marked decrease in eicosanoid production, the LC *n*-3 PUFAs acts promoting a change in the class of eicosanoids produced, without, however, completely abolishing those produced from AA. In addition, the inflammatory pro-resolution lipid mediators resolvins, maresins and protectins produced from the LC *n*-3 PUFAs DHA and EPA could control the tissue injury resulting from the exacerbated activation of the immune response [30]. Pro-resolvins are a class of lipid mediators that act in the resolution of inflammation [71]. E-series resolvins (RvE) are generated from EPA, D-series resolvins (RvD) from DHA, and protectins and maresins from DHA. The synthesis of these pro-resolvins also involves the COX and LOX pathway [72, 73].

Recently was demonstrated that trypomastigotes and amastigotes of *T. cruzi* produce the pro-resolving lipids RvD1, RvD5, and RvE2. It has been reported that plasma RvD1 levels are elevated in *T. cruzi* infected mice and, at least in part, it is possible that this RVD1 is from the parasite itself. This mechanism suggests another way of how the parasite can modulate the environment in its favor. This modulation of the immune response by the parasite may be important and contribute to the perpetuation of the infection into the chronic phase [74].

Therefore, the elucidation of the more specific mechanisms involved with the protective effects of *n*-3 PUFAs on *T. cruzi* infection (**Figure 2C**) are important aspects to be investigated. Considering the discussion presented here, as well as all points raised in the scientific literature, it is a reasonable to consider that the immune modulation exerted by LC *n*-3 PUFAs supplementation actually favors the host and may represent a perspective for the supplementary treatment of patients affected by Chagas disease.
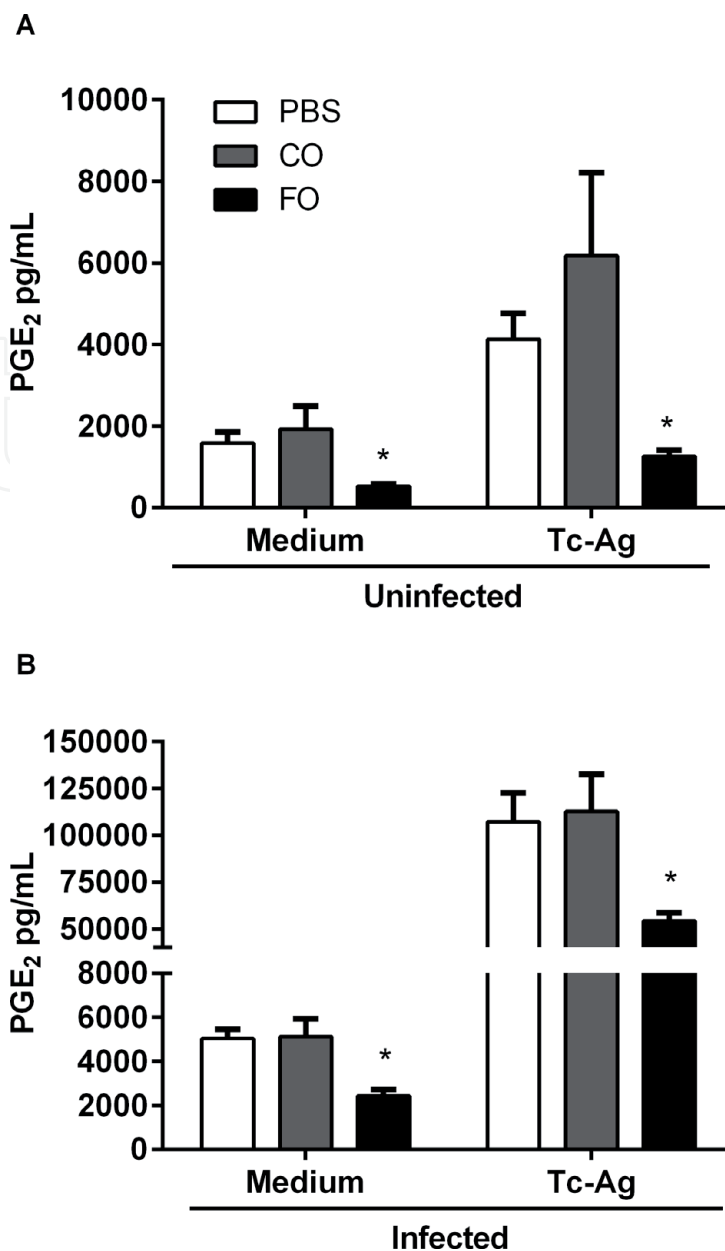
Figure 3.
Effects of fish oil supplementation on production of PGE2 by spleen cells from mice infected with T. cruzi. From 15 days before T. cruzi infection to the 7th dpi, C57BL/6 mice were supplemented by gavage with 0.6% (v/w) PBS, corn oil, or fish oil. C57BL/6 mice were infected with 5×10^3 blood trypomastigotes T. cruzi (Y strain). Splenocytes (5×10^6 cells/well) from uninfected (A) or T. cruzi-infected mice (B) were cultured with and without T. cruzi antigen (Tc-Ag). Supernatants were harvested after 8 hours, and PGE2 was quantified in supernatants by EIA. The results are expressed as means ± SEM from four animals per group and are representative of two independent experiments. Means not sharing letter are significantly different ($P<0.05$, 2-way ANOVA with Bonferroni post-test). Original publication [22].

5. Conclusion

The immunomodulatory effects of long-chain omega-3 polyunsaturated fatty acids (LC n-3 PUFA) are currently widely known. Dietary supplementation with LC n-3 PUFAs has been used as a complementary treatment in inflammatory diseases. However, the effects of daily supplementation with LC *n*-3 PUFAS on host resistance to infectious disease, such as the *T. cruzi* infection, are still poorly understood. Studies using a well-established mouse model of this human disease showed that fish oil supplementation improves de clinical course *T. cruzi* infection during the acute phase of infection. In fact, the potential benefits of LC *n*-3 PUFAs supplementation in humans have been the subject of recent clinical trials. The

modulation of the immune response by LC *n*-3 PUFAs, mainly through the change in eicosanoids patterns produced during *T. cruzi* infection, could be one mechanism that results in improvement of the host response. However, more studies are necessary to determine whether or not oral supplementation with LC n-3 PUFA could benefit humans diagnosed with Chagas disease.

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Conflict of interest

The authors declare that there are no conflicts of interest.

Notes/thanks/other declarations

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