

CYTOKINES IN HIV-POSITIVE INDIVIDUALS WITH HYPERTRIGLYCERIDEMIA MAKING USE OF OMEGA-3

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ABSTRACT

Currently AIDS is considered a chronic disease controlled with low morbidity and mortality. Antiretroviral therapy has been effective, but associated with serious adverse metabolic effects, including the epidemiological hypertriglyceridemia. Trials demonstrate correlation between elevated triglyceride levels, changes in adipocytokines and coronary artery disease. The use of omega-3 fatty acid (w -3) has been advocated for hypertriglyceridemia, though without consensus. Objectives: To assess the effect of omega-3 fatty acid in patients with HIV on antiretroviral therapy (HAART) with triglyceride levels between 200 and 400 mg / dl, correlating with the levels of adipocytokines. 17 patients of both sexes with HIV / AIDS using antiretroviral drugs were studied in Specialized Outpatient Service of Infectious Domingos Alves Meira-UNESP, and divided into 2 groups (G 1 and G 2) on two occasions (baseline and after 4 months) all with the same nutritional guidance and physical activity. Omega-3 has been recommended in G1. In both groups were evaluated: anthropometric profile, erythrocyte, lipid and immune. Of the 17 studied, 7 were in Group 1, 43% were female, 46.1 ± 19.1 years old, and Group 2 consisted of 10 patients, 40% were female, 54.5 ± 25 4 years of age. Overweight occurred in both groups, with a tendency to not very significant improvement in Group 1 after 4 months, and in Group 2 there was a slight weight increase in M2. Waist circumference (WC), lean mass, body fat, body water, erythrocyte, and immunological profile showed no significant differences between groups. Total cholesterol and triglycerides showed a tendency to decrease in M2 in both groups, LDL increased slightly in Group 1 in M2. The adipocytokines showed trends to decrease. There was a significant correlation between the index values of body mass and CC. Although the results were not significant, the use of omega-3 associated with nutritional guidance and physical activity showed a trend of improvement in lipid and anthropometric levels, and cytokine profile. Accordingly, further studies with a larger number of patients, longer follow-up and larger doses of omega-3 should be made for the control and prevention of Cardiovascular Diseases.

INTRODUCTION

Since the beginning of the epidemic, there was a significant advance in drug therapy used to fight this disease, with reductions in morbidity and mortality, as well as decrease the numbers of opportunistic infections and hospitalizations [1,2]. However, Shikuma [3] mentions that the protease inhibitors used in AIDS therapy have been

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associated with serious adverse metabolic effects, including peripheral lipodystrophy and insulin resistance and in some cases, type 2 diabetes, dyslipidemia and hypertriglyceridemia, causing great difficulty for these patients. They are also known for interfering with various cytokines such as tumor necrosis factor (TNF- α), interferon alpha (IFN- α), interleukin 1 (IL-1) and interleukin 6 (IL-6), which are both involved in immune reconstitution as lipid manipulation, due to the increased survival of individuals for treatment, greater exposure to risk factors for coronary artery disease (CAD) [4], associated with the use of IP as well as the HIV infection itself, and the onset of dyslipidemia occurs [5].

Hypertriglyceridemia has been considered the hallmark of HIV therapy - [6,7] associated with dyslipidemia. HIV patients with triglyceride levels above 500 mg / dl have fibrates indication. The great challenge for doctors is in the management of patients with HIV and hypertriglyceridemia with levels between 200 mg / dl, 500 mg / dl to whom there is still no drugs indication, but already have high levels. The omega-3 fatty acids are polyunsaturated lipids and have been indicated in this situation, although its performance and mechanisms remain ill-informed, and it is worth considering the possible relation between adipocytokines and tissue levels of triglycerides and use of omega -3 in these [8] patients.

Wohl et al [9] quotes that omega-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are one of two classes of essential fatty acids. The omega-3 is derived from marine source; fish oil has been shown to reduce triglyceride levels in fasting and postprandial and the use of statins in people without HIV infection [10]. The dose of omega-3 was approved and variable in 3-9 grams per day, and 8 well tolerated by patients, however, when administered for a long period, it seems to reduce hypertriglyceridemia with no apparent effect differential [11]. Although the use of this fatty acid has been indicated, its actual mechanism and association with inflammatory cytokines are unknown, particularly adipocytokines.

It is known that HIV infection triggers an inflammatory response in the body, and that the use of antiretroviral medications can contribute to metabolic alterations and associated changes in body composition and can influence the immune lipid profile. Adipose tissue behaves as a dynamic endocrine organ and is considered the largest organ of the body that secretes adipocytokines (leptin, adiponectin, TNF- α , IL-6 adiponectin, resistin, angiotensinogen, and plasminogen activator inhibitor). These are related directly and indirectly in processes that contribute to atherosclerosis, hypertension, insulin resistance and dyslipidemia, ie, they represent the link adiposity, metabolic syndrome and cardiovascular disease [12]. Other studies have shown that cytokines involved, especially in the early stages inflammatory response, which culminates in atherosclerosis, are the IL-1, IL-6, TNF- α

and IL-8, and the TNF- α inhibits markedly the action of lipoprotein lipase, which is responsible for lysis of triglycerides from the diet, fatty acids and glycerol 13. As cytokines act by regulating immune and inflammatory responses, when there is an imbalance of these cytokines, activation of macrophages and smooth muscle cells thereby promoting increased formation of atheroma, aggravating factor for cardiovascular disease [14].

Thus, it is important to know the efficiency of the use of omega-3 in hypertriglyceridemia and inflammation when serum lipid levels are high, the use of lipid-lowering [15]. An alternative to this situation is hyperlipemia dietary supplementation with fatty acids omega-3 that has been proven effective, besides the mere correction of lifestyle (diet and exercise to lower cholesterol) in the correction of hypertriglyceridemia induced by antiretroviral therapy in HIV - positive patients and there are few studies about such use [16]. Therefore, this study aims to investigate the role of adipocytokines in HIV individuals with hypertriglyceridemia in use of omega-3.

OBJECTIVE

Evaluating the serum levels of adipocytokines in HIV positive individuals with hypertriglyceridemia and comparing the levels of adipocytokines with the use of omega-3 through clinical nutritional assessment, lipid, glucose, haematological, immunological and virological profile in two moments: at the beginning and after 4 months.

METHODOLOGY

This study was conducted with 17 individuals of both sexes, aged over 18 years old, confirmed diagnosis of HIV and hypertriglyceridemia, seen at Hospital Dia AIDS (SAE-HD / AIDS), by the Foundation for the Medical and Hospital Development (Hospital FAMESP), at the Botucatu Medical School (FMB) Hospital Complex - UNESP. Individuals who participated in this study were previously informed about the procedures, submitted and signed consent for their participation and agreement documents, pursuant to Resolution No. 196/96 on "Research Involving Human Subjects", by the Health Council of the Ministry of Health. This study was approved by the Ethics and Research (CEP). In Specialized Infectious Outpatient Service at Domingos Alves Meira-UNESP, the records and information systems of examinations of individuals were analyzed, verifying the figures for recent lab tests, the presence of co-infections, current HAART and other medicines used to evaluate the possibility of inclusion of the individual in research. Among the participants, a consultation was held with a questionnaire and laboratory tests, lipid, glycemic, immunological and virological profile in clinical laboratory FMB / UNESP and the cytokines at Tropical Diseases Laboratory by the technique of ELISA, using commercial kits R & D $\text{\textcircled{R}}$ Systems, Minneapolis, MN, USA. Patients of



both sexes were included in the study, with a diagnosis of HIV confirmed by ELISA (Enzyme Linked Immuno Sorbent Assay) with hypertriglyceridemia with serum triglyceride levels greater or equal to 200 mg / dl and less than 400 mg / dl, who have been being treated with the same HAART. The study was begun by separating them into two groups: Group 1 G 1 (nutritional guidance and physical activity orientation, added the use of omega-3 (fish oil) and Group 2 - G2 (dietary guidance, orientation activity physical). Anthropometric and bioimpedance, lipid profile, immunological profile and nutritional counseling were conducted in two stages: inicial moment (M1) and final moment (M2). During the four months that the patients consumed the capsules of omega-3, which were distributed in monthly consultations by nutritionist. Regarding the statistical analysis, the results were analyzed by the Group for Research Support of the FMB - UNESP. Data were expressed as mean and standard deviation stratified by groups and times. Comparisons between means were made using analysis of variance and repeated measures, considering the group and time as main effects and group x time interaction. When the interaction was significant by Tukey test for effects nested set (group within time or vice versa) is made. Subsequently, the Pearson correlations for all variables were obtained and stratified by group and time. All analyzes were performed using SAS for Windows, version 9.2

RESULTS

Among the patients, seven were in Group 1, 43% female, mean age 46.1 ± 19.1 years and 57% were smokers, and in Group 2, consisted of 10 patients, 40%

were female, average age of 54.5 ± 25.4 years and 30% were smokers (Table 1). Both groups were using antiretrovirals (protease inhibitors, inhibitors Nucleoside Reverse Transcriptase Inhibitors and Non-Nucleoside Reverse Transcriptase).

Among the various indicators studied in relation to anthropometric profile, the patients presented with overweight in both groups, showing a not very significant improvement in Group 1 after 4 months in the M 2, Group 2 and a slight increase in the weight of the M1 for M2 (Table 1).

Waist circumference showed no significant differences in both groups, but in group 1 there was a tendency for decreasing in M2, compared to Group 2 (Table 1). As the use of bioimpedance, lean mass groups are appropriate, but fat mass showed up above the recommended, up to 25 kg and 20 kg for women men (Table 1), although both showed no statistical differences. The practice of physical activity at baseline was not reported by 4 patients in group 1 and 6 in group 2, but after four months of study and guidance all patients in both groups reported walking at least 2 times a week.

Regarding the test, the erythrocyte profile showed only slight increase of lymphocytes in Group 1 after 4 months of use of omega-3 (Table 1). The lipid profile in both groups had no statistically positive differences, total cholesterol and triglycerides had a tendency to decrease in M2 in the two groups, since the LDL increased slightly in Group 1 in M2 possibly by the use of omega-3. Blood glucose also showed no differences, but had a tendency to increase in Group 2 after 4 months (Table 1).

Table 1. Erythrocyte, biochemical, immune, and anthropometric profile and its mean and standard deviation of 17 HIV positive individuals with hypertriglyceridemia in HAART treated at SAE of Infectious Diseases "Domingo Alves Meira" -FMB UNESP.

Variables	G 1(n7)		G 2(n10)	
	M1	M2	M1	M2
Age (years)	$46,1 \pm 19,1^*$		$54,5 \pm 25,4^*$	
Females	43%		40%	
Males	57%		60%	
Tobacco	57%		30%	
BMI	$26,96 \pm 5,44$	$26,87 \pm 6,14$	$27,82 \pm 2,95$	$28,51 \pm 3,16$
WC	$91,00 \pm 13,13$	$90,57 \pm 15,18$	$97,40 \pm 10,59$	$97,60 \pm 11,26$
Lean mass	$68,92 \pm 12,16$	$67,81 \pm 9,19$	$67,70 \pm 5,02$	$67,83 \pm 6,62$
Fat mass	$31,08 \pm 12,16$	$32,19 \pm 9,19$	$32,30 \pm 5,02$	$32,11 \pm 6,69$
Hemoglobin (mg/dl)	$14,54 \pm 1,24$	$13,63 \pm 4,20$	$15,16 \pm 1,32$	$15,40 \pm 1,16$
Hematócrit (mg/dL)	$42,64 \pm 3,66$	$40,04 \pm 11,97$	$42,80 \pm 3,82$	$44,10 \pm 3,11$
Lymphocyte (mg/dl)	$1745,31 \pm 885,52$	$2037,66 \pm 1516$	$2075,60 \pm 500,86$	$2106,10 \pm 716,10$
T CD4 (mm ³)	$663,57 \pm 462,83$	$611,14 \pm 257,01$	$665,80 \pm 240,69$	$720,20 \pm 214,81$
T CD8 (mm ³)	$1157,14 \pm 585,82$	$1064,57 \pm 551,76$	$717,70 \pm 313,69$	$1051,10 \pm 460,88$
Total Cholesterol (mg/dl)	$213,57 \pm 38,97$	$203,71 \pm 58,05$	$194,80 \pm 25,89$	$188,90 \pm 35,87$
LDL (mg/dl)	$103,49 \pm 27,19$	$113,71 \pm 57,19$	$105,72 \pm 27,10$	$100 \pm 32,52$
HDL (mg/dl)	$65,14 \pm 26,42$	$51,43 \pm 13,97$	$38,60 \pm 7,65$	$44,20 \pm 6,55$
Triglycerides(mg/dl)	$231,86 \pm 34,45$	$199,86 \pm 55,15$	$252,40 \pm 39,95$	$223,50 \pm 71,84$
Glycemia (mg/dl)	$88 \pm 14,94$	$83,14 \pm 9,44$	$96,10 \pm 22,57$	$108,10 \pm 54,52$



* HAART: highly active antiretroviral therapy; SAE: specialized outpatient service; FMB: Botucatu Medical School; n: number; G1: group 1; G2: group 2 M1: 1 point; M2: 2 time; BMI: body mass index, WC: waist circumference, CD4: CD4 T Lymphocyte; CD8: CD8 lymphocyte LDL: low density lipoproteins (low density lipoprotein); HDL: high density lipoproteins, $p < 0.001$.

Regarding cytokines and comparison and evolution of leptin, adiponectin there was similar conduct in the groups with and without use of omega-3, but adiponectin levels remained higher in group 1, ie with omega-3. Regarding leptin, changes were not observed. (Table 2). It is worth noting that in the levels of TNF α and IL6 it was not possible to assess significant differences between groups.

Table 2. Cytokines profile and its respective averages and standard deviation of 17 HIV positive individuals with hypertriglyceridemia in HAART treated at SAE of Infectious Diseases "Domingo Alves Meira" -FMB UNESP.

Variables	G1(n7)		G2(n10)	
	M1	M2	M1	M2
TNF α (pg/ml)	173,43 \pm 27	149,86 \pm 44,69	166,10 \pm 40,36	176,20 \pm 45,94
IL6 (ng/ml)	80,86 9 \pm , 53	65,57 \pm 23,15	77,40 \pm 9,86	71,70 \pm 13,72
Leptin(pg/ml)	209 \pm 36,78	183,71 \pm 47,35	239,50 \pm 73,07	217,10 \pm 64,12
Adiponectin(pg/ml)	437,43 \pm 96,39	396,29 \pm 64,10	490,50 \pm 267,60	499,50 \pm 254,83

* HAART: highly active antiretroviral therapy; SAE: Specialized Outpatient Service; FMB: Botucatu Medical School; n: number; G1: group 1; G2: group 2 M1: 1 point; M2: 2 time; TNF: tumor necrosis fact; IL6: interleukin 6 $p < 0.001$.

Figure 1. Individual analysis and comparison between the evolution of TNF α and IL6 from 17 HIV positive individuals with hypertriglyceridemia in HAART treated at SAE infectious disease "Domingos Alves Meira" - FMB UNESP. (... HAART antiretroviral therapy highly active. SAE Specialized Outpatient Service. FMB Botucatu Medical School. M1 M2 time 2 time 1 TNF: tumor necrosis factor, IL6: Interleukin 6).

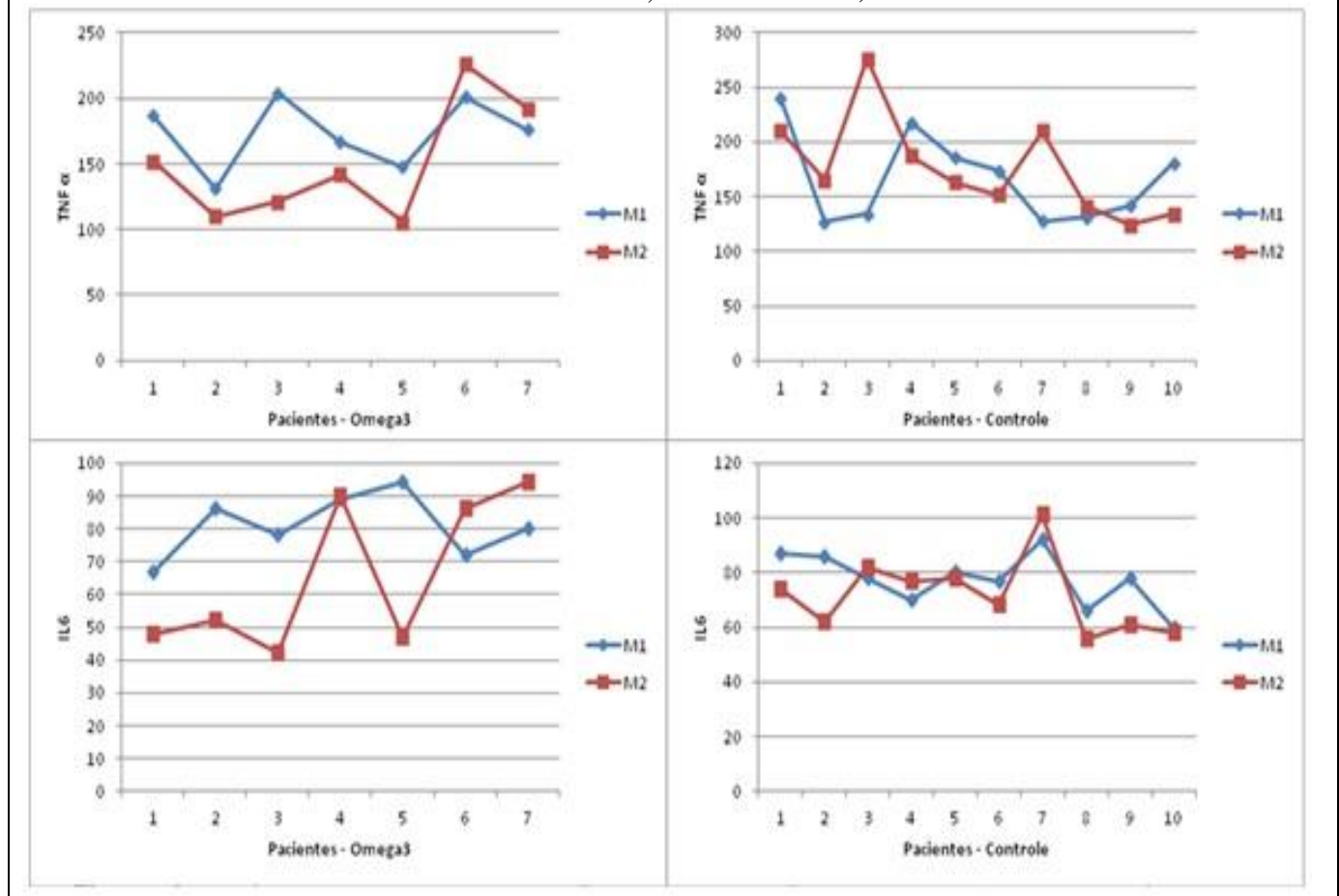
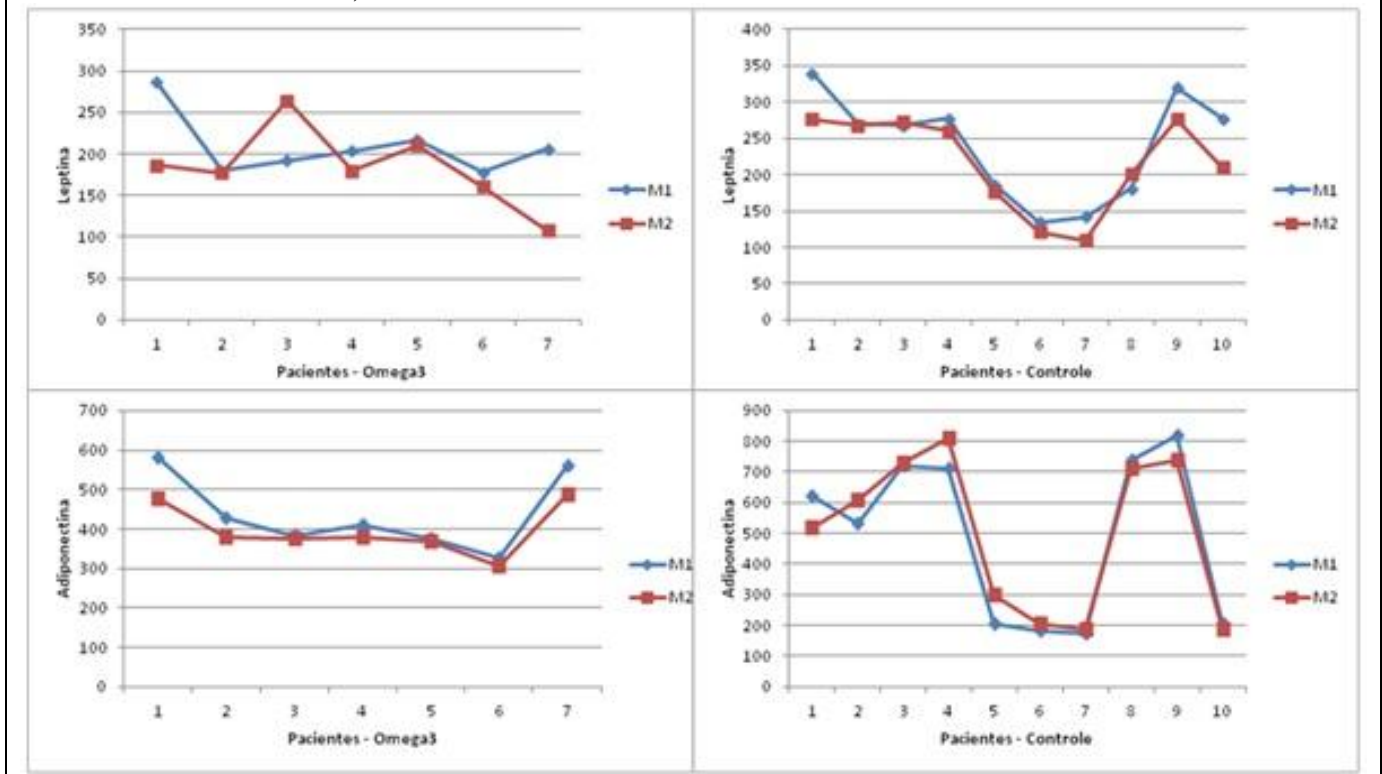


Figure 2. Individual analysis and comparison between the evolution Leptin and Adiponectin as the 17 HIV positive individuals with hypertriglyceridemia in HAART treated at SAE infectious disease "Domingos Alves Meira" - FMB UNESP. (HAART antiretroviral therapy of high activity. SAE specialized outpatient service. FMB – Botucatu Medical School . M1 M2 1 time 2 time)



DISCUSSION

Currently, AIDS is considered a chronic disease in which patients make use of antiretrovirals and have alterations in body composition and changes in lipid profile, particularly hypertriglyceridemia, which are factors associated with the risk of developing cardiovascular disease. The omega-3 has a protective and immunomodulatory effect, and can help reduce triglyceride levels and improves the immune profile. In this sense, the present study evaluated the use of omega-3 in patients with hypertriglyceridemia in HIV and antiretroviral use.

From the subjects studied there was a predominance of males in both groups, and age range was around 50 years old, which is the current distribution of this pathology. In addition, smoking is a factor that contributes to the worsening of dyslipidemia, it was present in 57% of subjects in the group intake of omega-3 fatty acid, which may contribute to the development of cardiovascular diseases.

Regarding anthropometric measurements and examination of bioimpedance, both groups were classified as overweight according to the Body Mass Index and the index showed high fat mass, besides, the circumference increased according to the criteria of the IDF 2005 [17]. Several authors [18,19] report that among the factors that

contribute to the onset of cardiovascular diseases, including hypertriglyceridemia, are obesity, increased waist circumference and body fat, which are prevalent in the population and should be identified. Overweight and obesity are associated with increased risk of developing chronic non transmitted 6 morbidities.

The erythrocyte and immune profile can vary widely in patients with HIV on antiretroviral use. In the present study no differences in the levels of erythrocyte were observed. Anemia, however, is common in HIV-infected individuals, occurring in approximately 30% of asymptomatic and 60% to 70% of those with AIDS, and is related to the quality of life and survival of these [20].

The counted serum lymphocyte also revealed that the patients were in good immune status in both groups. Intervention group in the number of lymphocytes of patients tended to increase after using omega-3 for four months, which may be the immunomodulatory effect of fish oil. Recently, a Spanish group reports the immunomodulatory effect of omega-3 fatty acids causing significant increase in the number of CD4 T lymphocytes, when used in the average dose 3-4 grams per day [21]. In the present study, there were no significant changes in CD4, CD8 and viral load in both groups were within



normal limits, but a study conducted in Italy on the CD4 count did not show statistically significant results for the mean 3-4 month treatment [8].

Another important factor in the evaluation of patients with HIV and hypertriglyceridemia is the knowledge of glycemic profile that can be changed by the effect of antiretroviral medication and the lifestyle [21]. Through the glycemic profile it is possible to discover changes that may lead to the onset of insulin resistance and type 2 diabetes mellitus, and these should influence the development of metabolic syndrome which is common in HIV positive patients. Both groups showed no changes in glycemic control initially, but in the group without omega-3 even after the guidelines tended to increase levels. Perhaps the omega-3 may be contributing to the maintenance of blood glucose levels.

Several studies have reported the use of antiretrovirals associated with the onset of dyslipidemia, particularly hypertriglyceridemia. In addition to high serum triglycerides, total and LDL cholesterol were higher in the intervention group, with the exception of HDL. In Group 2 both times the total cholesterol values were within the recommendations. These changes may appear to change body composition, ie, overweight and obesity, and both collaborate for the development of cardiovascular diseases and changes of inflammatory cytokines. Patients on ARVs have more atherogenic lipid profile than those without treatment, except in relation to the levels of HDL cholesterol [22], which agrees with the findings of the present study. Some studies have shown higher levels of triglycerides between patients on antiretroviral compared to no medication [24]. Guimarães 2007 [22] reinforces the fact that the use of antiretroviral therapy seems to be related to development of lipid abnormalities, either by direct action of drugs or which may cause changes in host-virus relationship.

In the present study, triglyceride levels were above the ideal, but with the use of omega -3 fatty acid levels tended to decrease more than the group that guided only healthy food and exercise, so the omega-3 is important to assist in reducing hypertriglyceridemia. Several studies show that high levels of triglycerides in serum are associated with four pathogenic conditions that accelerate atherosclerosis: decreased levels of HDL in serum; increased remnant lipoproteins; small elevation in LDL; increasing the thrombogenic conditions, and these factors suggest that the hypertriglyceridemia may be the cause of atherosclerosis [25,26]. Accordingly it is vital to early diagnosis of dyslipidemia and conduct.

The increase in HDL is a factor which delays the onset of atherosclerosis and consequently causes a decrease in the progression of coronary artery disease. In the present study, both groups showed no statistical difference in relation to HDL, which exerts a protective effect on antioxidant enzymes and thus may prevent initial inflammatory processes [26]. In the Brazilian study by

Caramelli and co-workers [23], hypercholesterolemia was present in 43% and hypertriglyceridemia in 53% of patients treated using protease inhibitors. The management of hypertriglyceridemia in these patients has been a major challenge for physicians and health care professionals. In this study, the selection of patients for intervention revealed great difficulties, and many were excluded because they presented sequelae of HIV, drug use and antilipemic medications, among others, which restricted the number of samples in that time period. Furthermore, although under the guidelines and recommendations by the nutritionist's work, it was difficult to get patient compliance, and accordingly, for greater control of the intake of omega-3 was conducted monthly count of capsules, which ensured that all patients were ingesting them correctly.

With the use of omega-3 during four months in the present study, we observed a tendency to decrease triglyceride levels. Wohl and colleagues [9] performed a randomized study with 52 patients with hypertriglyceridemia in antiretroviral use, and who received food and exercise for 16 weeks orientation, with or without the use acid fatty omega-3 (1750 mg EPA and 1150 mg DHA). In 16 weeks, the mean reduction in triglycerides in patients receiving fish oil was 19.5%, while the average decrease in not receiving fish oil was 5.7%, similar to the present study, no difference and was significantly increased levels of LDL.

A review of randomized controlled trials of patients with triglyceride levels above 150 mg / dl showed that among those who took omega-3 at doses 3-4 grams per day, triglyceride levels were reduced on average 29% [28,29]. These studies show that treatment with omega-3 is safe and effective, but can induce modest increase in HDL and LDL [30,31]. Raniere, 2007 [8] showed that triglyceride values decreased significantly after 6 months of therapy and guidance diet with 3 grams per day of omega-3 (TG: 290.35 ± 48.51 mg / dl vs. 223.05 ± 39.72 mg / dl, $p < 0.001$). This study shows that the time of supply of omega-3 may be an important factor in the response to its use. Therefore, omega -3 fatty acid, though it aids in lowering triglyceride levels and exert immunomodulatory effect, several mechanisms of action remain poorly understood [30].

Another important factor is the association between adipose tissue, hypertriglyceridemia, and cytokine production. In this sense, cytokines are altered by HIV itself, antiretroviral use and overweight. Adipose tissue functions as an endocrine organ and is capable of secreting a variety of substances, including hormones and cytokines such as leptin, adiponectin, TNF- α and interleukin - 6 [31].

TNF- α , IL6 and leptin are pro-inflammatory cytokines, and their levels are increased in adipocytes for obesity and in patients with type 2 diabetes, dyslipidemia, and HIV in our present study showed increased levels in most patients, and tended to decline after the use of omega-



3. They increase concomitantly with opportunistic infections in these patients, and this increase may exacerbate the reduction in HDL and LDL [32]. Some studies have shown that the aspect of these cytokines is increased in patients with HIV and increased fat redistribution, compared with those without this change [33,34]. Adiponectin is exclusively produced and secreted by adipose tissue and correlates negatively with body mass index, visceral fat and this one, in decreased levels in diabetic and obese. Patients in the present study levels showed no alterations in both groups. This cytokine has an anti-inflammatory and atherogenic effect, and its action decreases the excess of TNF α , IL-6 and leptin. However, these proinflammatory markers correlated with increased cardiovascular risk in HIV patients remains valid 35. The use of omega-3 showed a tendency to reducing the inflammatory cytokines, similarly to what happens with the triglyceride that can represent the protective and immunomodulatory role offered by this supplement.

Data from the present study agree with some authors who have not fully significant results [8,9,28,29]. In relation to quantification of cytokines and their association with hypertriglyceridemia and HIV, there are no studies. The fact of not having observed significant

results may be due to the small number of patients studied, dose of supplementation and follow up on the use of omega-3. Therefore its use led to a tendency to decrease the levels of cytokines (leptin, adiponectin, IL6 and TNF α) and triglycerides. Therefore, further studies should be conducted with the supplementation of omega-3, commitment to continuously feed rehabilitation, and physical activity which contribute to the improvement of quality of life.

CONCLUSION

The omega-3 fatty acid used in patients with HIV and hypertriglyceridemia showed a tendency to decrease serum triglycerides and serum levels of cytokines such as leptin, IL6 and TNF α with the use of omega-3, revealing its immunomodulatory effect. However there is need for further studies to clarify and define the mechanisms of action of omega-3, longer follow-up, higher dose and more patients.

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CONFLICT OF INTEREST:

The authors declare that they have no conflict of interest.

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