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Effectiveness of n-3 fatty acids in the treatment of hypertriglyceridemia in HIV/AIDS patients: a meta-analysis

Efetividade de ácidos graxos n-3 no tratamento da hipertrigliceridemia em pacientes com HIV/AIDS: uma meta-análise

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Abstract *Hypertriglyceridemia is common in antiretroviral therapy-treated patients and Omega 3 fatty acids are being used as a intervention in reducing serum triglycerides (TG) in these patients. The objective of this study is to evaluate the effectiveness of the use of Omega 3 in the treatment of hypertriglyceridemia in HIV/AIDS patients on antiretroviral therapy. This study is a systematic review with meta-analysis of randomized clinical trials. Electronic databases – PubMed, Cochrane and Lilacs were researched. Fifty one articles were encountered. Nine were added to the meta-analysis. The reduction of triglycerides level was -77.55 mg (IC of -121.85 to -33.25) in Omega 3 groups. The analysis considering trials with more than 1000 mg of EPA/DHA included seven studies and the heterogeneity dropped to 0%.The reduction of combined averages was -101.56mg (IC of -145.76 to -57.37). The analysis considering trials with patients that had more than 200 mg/dL of initial triglycerides included also seven trials and the heterogeneity dropped to 0%. The reduction of combined averages was -114.15 mg (IC of -162.34 to -65.97). EPA/DHA supplementation reduces serum triglycerides levels in patients with HIV/AIDS-associated hypertriglyceridemia in stable use of antiretroviral therapy.*

Key words *HIV, HAART, Triglycerides, Omega 3 and fish oil*

Resumo *A hipertrigliceridemia é comum em pacientes tratados com terapia antirretroviral e os ácidos graxos ômega 3 estão sendo usados como uma intervenção na redução triglicérides séricos (TG) nesses pacientes. O objetivo deste estudo é avaliar a eficácia do uso do ômega 3 no tratamento da hipertrigliceridemia em pacientes com HIV/Aids em terapia antirretroviral. Este estudo é uma revisão sistemática com metanálise de ensaios clínicos randomizados. As bases de dados eletrônicas – PubMed, Cochrane e Lilacs foram pesquisadas. Cinquenta e um artigos foram encontrados. Nove incluídos na metanálise. A redução do nível de triglicerídios foi -77.55 mg (IC de -121,85 a - 33,25) no grupo com Omega 3. A análise considerando ensaios com mais de 1000 mg de EPA/DHA incluiu sete estudos e a heterogeneidade caiu para 0%. A redução das médias combinada foi -101.56 mg (IC de -145,76 a -57,37). A análise considerando ensaios com doentes que tinham mais do que 200 mg/dL, de triglicéridos iniciais incluiu também sete ensaios e a heterogeneidade caiu para 0%. A redução das médias combinada foi -114.15 mg (IC de -162,34 a -65,97). A suplementação de EPA/DHA reduz níveis de triglicérides séricos em pacientes com hipertrigliceridemia associada ao HIV/AIDS em uso de terapia antirretroviral estável.*

Palavras-chave *HIV, HAART, Triglicerídeos, Ômega 3 e óleo de peixe*

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Introduction

Highly activity antiretroviral therapy (HAART) is reducing the morbidity and mortality of HIV-infected patients. With improved prognosis, the disease's chronic aspect started to be handled with[1,2]. However, treatment is associated to adverse reactions and HIV associated lipodystrophy syndrome characterized by dyslipidemia, glycemic alterations and morphologic alterations as lipoatrophy and lipohypertrophy[3].

In case of dyslipidemia, when associated to HIV-infection, it occurs low HDL levels, total cholesterol and LDL increase (TC) and rise of triglycerides, conditions that favor the risk of cardiovascular disease[4,5]. A few observational studies revealed that the incidence of cardiovascular event in HIV-infected patients on ART is higher than in the overall population[6,7].

Hypertriglyceridemia is one of the most frequent metabolic alterations in ART patients[8]. In a transversal study with 788 patients' cohort, the authors identified the prevalence of 56% of hypertriglyceridemia[9].

It has been discussed the effect of Omega 3 fatty acids in metabolic complications in ART patients. Almeida et al., in a review, concluded that Omega 3 supplementation resulted in substantial reduction of serum triglycerides levels[10]. In 2012, a new review showed that the reduction of triglycerides with Omega 3 fatty acids supplementation was the nutritional intervention that most gathered substantial scientific evidences[11].

In a meta-analysis published by Oliveira et al.[12] in 2011 with four controlled trials evaluating the use of Omega 3 fatty acids in the reduction of serum triglycerides in ART HIV-patients, it was observed a reduction of -80.34 with interval confidence of (IC of -129.08 to -31.60) in Omega-3 treated groups. In another meta-analysis where the effects of dietetic intervention in HIV dyslipidemia were analyzed it was observed a reduction of 99.11 (IC of -138.93 to -59.29) in triglycerides of the Omega 3-treated group[13].

In another study of Jacobson[14], the author discuss that the degree of TG reduction would be associated on the initial levels of triglycerides and the dose of EPA/DHA used.

There was no uniformity across clinical trials in the dosage of the supplement used, with a variation of 900 to 4000 mg/day of EPA/DHA. The same thing happens with the initial triglicerides dosage[15,16].

New clinical trials were published[16-18], and better answers are necessary to the questions mentioned above.

The aim of this study is to evaluate the effectiveness of the use of omega 3 fatty acids in the treatment of hypertriglyceridemia in HIV/AIDS patients on HAART.

Method

This study consists in a systematic review with meta-analysis of randomized clinical trials to assess the use of Omega 3 fatty acids for the treatment of hypertriglyceridemia in HIV/AIDS patients.

Studies with HIV/AIDS male and female, any ethnicity adult individuals on stable use of ARV's with Omega 3 fatty acids-based interventions, at any dosage, compared with control group placebo and serum triglycerides as outcome were included. Studies comparing equivalence or superiority of n-3 supplement the drugs were excluded.

The research was made in electronic databases – PubMed, Cochrane Central of Clinical Trials, and Lilacs, using the terms: HIV, HAART, triglycerides, hypertriglyceridemia, Omega3 and fish oil. The searches were made between May 2013 and August 2014, and the terms were used in the follow combination, aiming to find the greatest number of studies: HIV, Hypertriglyceridemia, omega 3; HIV, Hypertriglyceridemia, fish oil; HIV, triglycerides, omega 3; HIV, triglycerides, fish oil; HAART, Hypertriglyceridemia, omega 3; HAART, Hypertriglyceridemia,fish oil; HAART, triglycerides, omega 3; HAART, triglycerides, fish oil. Articles were obtained from specific bibliographic references in manual search too. The quotes identified by the researchers were selected by two independent reviewers.

Jadad Scale[19] was adopted to evaluate the quality of the articles comprehending the randomization (1 point to randomized plus 1 for adequate randomization), blinding (1 point to blinding plus 1 for adequate blinding) and losses (only 1 point). So the total sum of points is five and five is the better classification. However, such classification was applied only to discuss different results of each study and not to discard them.

Portions of the data were extracted independently by two reviewers.

Differences of weighted averages by the inversion of the variance of the study[20] to evaluate the magnitude of the effect of the intervention and their respective intervals of confidence (IC) of 95% were used. The variable of the outcome was the final value of the triglycerides of each group. Initially, combined averages method were esti-

mated using the fixed effects method[20]. In case of heterogeneity, Dersimonian & Laird[21] random effects model was used. The presence of heterogeneity was evaluated per the methods suggested by Deeks et al.[20].

Initially, a graphic exploratory analysis was performed based in the visual inspection of the charts (*forest-plot*). Later, the chi-square test (χ^2) of homogeneity was calculated.

Because of the limitation of the test χ^2, the heterogeneity was investigated as well through statistic I^2 proposed by Higgins & Thompson[22]. Values below 30% mean mild heterogeneity, intermediate values of 30% to 50%, moderate and above 50%, an elevated level of heterogeneity.

Multivariate models of meta-regression[23] were adjusted to investigate possible sources of heterogeneity across the studies' results.

It was adopted the sensibility analysis to explore the robustness of the results. This analysis consists in the repetition of the procedures, excluding, for example, non-published studies and of low methodological quality.

Stata 10.0 SE[24] software was used for statistical analysis.

Results

A total of 51 articles were encountered. At Pubmed 33, Cochrane 15, Lilacs 2 and 1 article as reference of references. Of a total of 51 articles, only 9 met the eligibility criteria previously defined and were included in the meta-analysis (Figure 1).

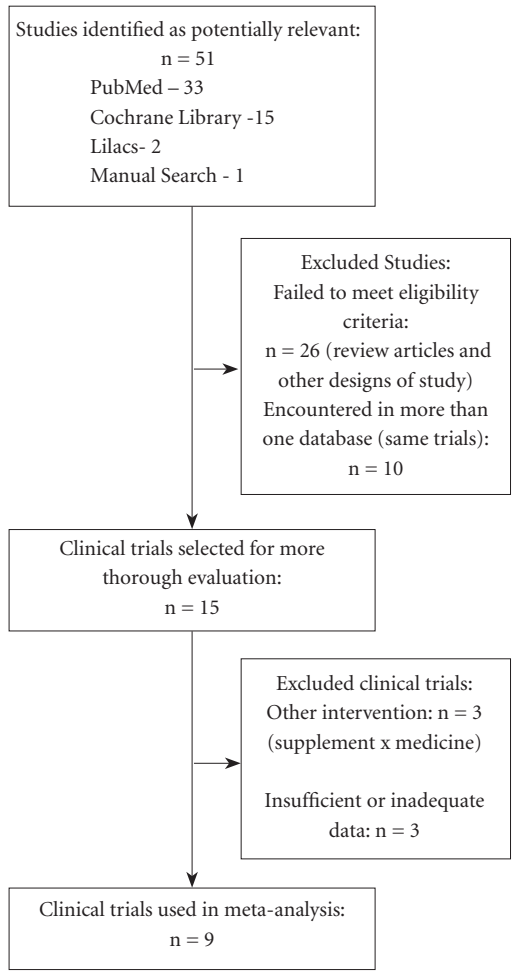


Figure 1. Flow chart with stages of obtaining of results.

Of the nine (9) clinical trials included in this meta-analysis with total of 448 patients, five (5) consider diet together with intervention[17,25-28] and one of them adopted diet and physical work out[28]. The other four (4) did not address co-interventions. The result of the quality analysis according to Jadad Scale was three trials (3) with five points, three trials (3) with four points and three trials (3) with Three points.

Six studies accepted the stable use of hypolipemiants for a minimum period (prior to the beginning of the study) of 8 weeks[18]; 3 months[15,29]; 6 months[25]; one of them accepted the use of statin, but excluded who were on fibrates for 6 weeks before the beginning of the study[28]; and on another, the use of fibrate or niacin was allowed, but the use of niacin for less or equal to 3 months prior to the beginning of the study was exclusion criteria[26]. Various TARV regimens were described, using protease inhibitors (PIs), NRTI (nucleoside analog reverse-transcriptase inhibitors) and NNRTI (non-nucleoside analog reverse-transcriptase inhibitors) in various combinations; and the stable use for a period of ≥ 2 months[27]; ≥ 3 months[16,18,26,28,29]; ≥ 6 months[15,17,25] was inclusion criteria.

Supplements used and dosages of EPA/DHA (eicosapentaenoic acid and docosahexaenoic acid) per day were:

Omacor® – 3360 mg[26,29];
Maxepa® – 2700 mg[25],1800 mg[27];
Lovaza® – 3360 mg[18];
Coromega® – 2900 mg[28];
Salmon oil – 900 mg[15];
Fish oil – 4000 mg[17], 900 mg[16]

The studies included in this revision are shown in Chart 1.

Chart 1. Data summary of clinical trials included in the meta-analysis.

Author/ Year/ Country	Method/ timing (author/used)	Intervention (n)	Control (n)	Jadad	Results (tg)			
					I		C	
					mg/dL(SD)	mmol/ L(SD)	mg/dL(SD)	mmol/ L(SD)
Baril JG et al.[15], 2007. Canada	Clinical Trial, randomized, controlled, crossover. 24 weeks (author). 12 weeks (used).	Salmon oil. EPA/DHA - 540/360mg. n = 26	Did not use placebo, did not receive oil (salmon) in the 12 initial weeks, but from 12th -24th weeks. n = 31	3	380,5 (203,5), reduction TG. P = 0.04	4.3 (2.3)	433.6 (212.3)	4.9 (2.4)
					I		C	
					mg/dL (SD)	mmol/L (SD)	mg/dL (SD)	mmol/ L(SD)
Peters BS et al.[26], 2012. England	Clinical trial, randomized Double-blind, controlled. 12 weeks.	Hypocholesterinic diet in use of fibrate or niacin. Omacor®. EPA/DHA - 1840/1520mg. n = 23	Hypocholesterinic diet in use of fibrate or niacin + placebo. n = 25	5	342.4 (168.1), reduction TG. p = 0.02	3.78 (1.90)	425.6 (272.5)	4.81 (3.08)
					I		C	
					mg/dL (SD)	mmol/L (SD)	mg/dL (SD)	mmol/ L(SD)
Carter et al.[25], 2006. Australia	Clinical trial, randomized Double-blind, controlled. 14 weeks.	Maxepa®. EPA/DHA - 1620/1080mg. n = 5	Dietary guidance for 6 weeks (NHFG) placebo (olive oil). n = 6	4	203.5 (163.7), reduction TG. p = 0.04	2.3 (1.85)	361.1(163.7)	4.08 (1.85)
					I		C	
					mg/dL (SD)	mmol/L (SD)	mg/dL (SD)	mmol/L (SD)
De Truchis et al.[27], 2007. France	Clinical trial, randomized Double-blind, controlled. crossover. 16 weeks (author). 8 weeks (used).	Maxepa® EPA/DHA - 1080mg/720mg. n = 58	4 weeks diet (AHA) placebo. n = 62	5	340 (180), reduction TG. p = 0.003	3.8 (2.30)	480 (310)	5.4 (3.5)
					I		C	
					mg/dL (SD)	mmol/L (SD)	mg/dL (SD)	mmol/L (SD)
Wohl et al.[28], 2005. USA	Clinical Trial, randomized, controlled. 16 weeks (author). 4 weeks (used).	Coromega®. EPA/DHA - 1750/1150mg. n = 24.	Diet and physical activity (AHA), no placebo. n = 20	3	306 (162), redução TG. p = 0,007	3.4 (1.8)	503 (421)	5.6 (4.7)
					I		C	
					mg/dL (SD)	mmol/L (SD)	mg/dL (SD)	mmol/L (SD)
Thusgaardet al..[29], 2009. Denmark	Clinical trial, randomized Double-blind, controlled. 12 weeks.	Omacor® EPA/DHA - 1840/1520mg. n = 25	Placebo, 2 pills, 2g corn oil 2x/day. n = 23	4	134.5 (85.8), reduction TG. p = 0.03	1.52 (0.97)	178.7 (170.7)	2.02 (1.93)

it continues

Chart 1. continuation

Author/ Year/ Country	Method/ timing (author/used)	Intervention (n)	Control (n)	Jadad	Results (tg)			
					I		C	
					mg/dL (SD)	mmol/L (SD)	mg/dL (SD)	mmol/L (SD)
Capili & Anastasi[17], 2013. USA	Clinical trial, randomized Double-blind, controlled. 10 weeks (author). 8 weeks (used).	Diet (NCEP-TLC). Fish oil. EPA/DHA - 2400mg/1600mg n = 8	Diet (NCEP-TLC) placebo n = 10	4	169 (133), reduction TG. p = 0.013	1.90 (1.50)	289 (129)	3.26 (1.45)
					I		C	
Oliveira et al.[16], 2014. Brazil	Clinical Trial, randomized, controlled. 24 weeks.	Fish oil. EPA/DHA - 540mg/365mg. n = 31	Placebo, 3g soy oil/day n = 35	3	mg/dL (SD)	mmol/L (SD)	mg/dL (SD)	mmol/L (SD)
					141.7 (59.7), Non-significant reduction TG When compared with GC. p = 0.613	1.60 (0.67)	158.6 (59.0)	1.79 (0.66)
					I		C	
Paranandi A et al.[14], 2014. USA	Clinical Trial, randomized, controlled. Crossover. 28 weeks (author) Washout (4 weeks) 12 weeks (used).	Lovaza®. EPA/DHA - 1860/1500mg (12 weeks) n = 17	Placebo (12 weeks.), washout (4 weeks) and 4 pills of Lovaza® (12 weeks). n = 19	5	mg/dL (SD)	mmol/L (SD)	mg/dL (SD)	mmol/L (SD)
					215.6 (149.4), reduction TG. p = 0.001	2.43 (1.68)	335.6 (314.2)	3.79 (3.55)

A (eicosapentanoic acid), DHA (docosahexaenoic acid), PUFA (n-3 polyunsaturated fatty acid). Omacor® (Abbot), Maxepa® (Seven Seas Health Care Ltd), Coromega® (European Reference Botanical laboratories), Lovaza® (GlaxoSmithKline Pharmaceuticals). NFHG (National Heart Foundation Guidelines), AHA (American Heart Association), NCEP-TLC (National Cholesterol Education Program - Therapeutic Lifestyle Changes). To converte TG mmol/L to mg/dL, divide by 0,0113.

Effect of the Omega 3 fatty acids on triglycerides in individuals with HIV/AIDS associated hypertriglyceridemia

Of the studies encountered and considering those with sufficient data for calculation purposes, nine clinical trials evaluated the outcome of interest. Heterogeneity measured by I^2 of Higgins & Thompson[22] was 43.7%. The results of each study, their respective intervals of confidence (IC) of 95% and the summary measure are shown in Graphic 1. The reduction of combined averages through random effects was -77.55 mg/dL (IC of -121.85 to -33.25; p = 0.001), that can be interpreted as presence of significant reduction of triglycerides of the Omega 3group.

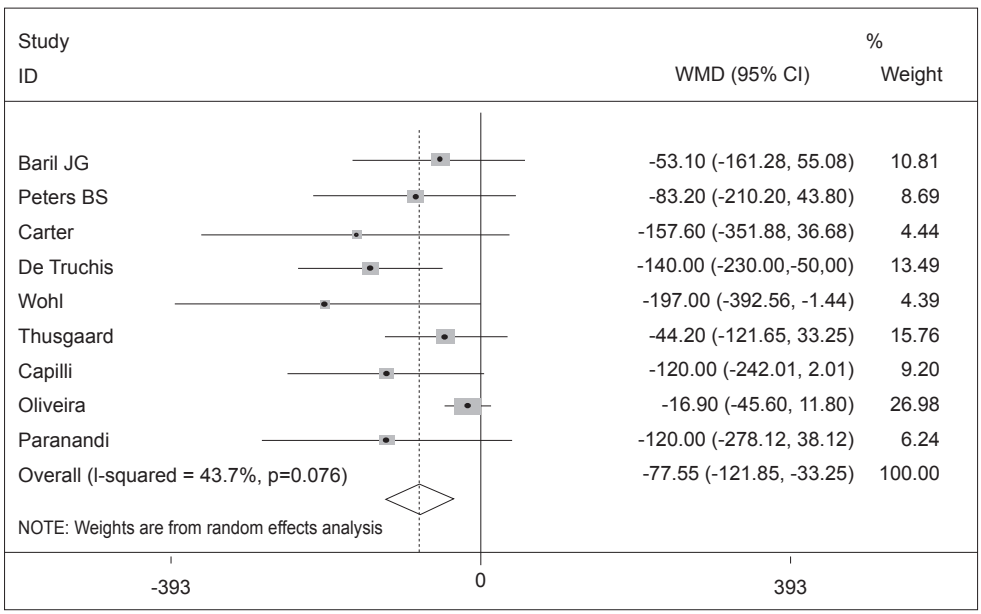
Year variables, classification of Jadad et al.[19], EPA and DHA dosage and initial triglycerides were analyzed to evaluate heterogeneity. However, none of the variables used explained the heterogeneity.

As the AHA cardioprotective recommended dosage is approximately 1g/d and the recommended dosage to reduce triglycerides levels is 2 to 4g/d[30] it was performed the analysis of subgroups considering studies with more than 1000 mg of EPA/DHA. Of the nine studies included, seven used more than 1000 mg of EPA/DHA and, when these seven were analyzed, the heterogeneity measured by I^2 of Higgins & Thompson[22] dropped to 0%. The results of each study, their respective intervals of confidence (IC) of 95%

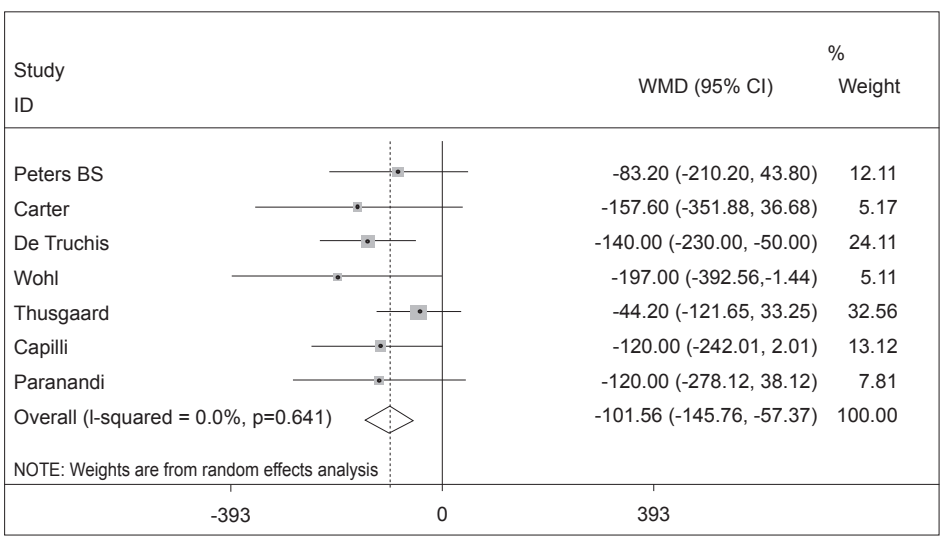
and the summary measure are shown in Graphic 2. The reduction of combined averages through the random effects was

-101.56 mg/dL (IC of -145.76 to -57.37; p= 0.00), which can be interpreted as presence of significant reduction of triglycerides of the group that used more than 1000 mg of EPA/DHA.

Was performed the analysis of subgroups in studies with patients that had more than 200 mg/dL serum triglycerides in the beginning of the study, a value defined as elevated level of triglyceride[31]. Of the nine studies used in this meta-analysis, seven included patients with initial average triglycerides over 200 mg/dL and



Graphic 1. Effectiveness of Omega 3 fatty acids to treat HIV/AIDS associated hypertriglyceridemia.



Graphic 2. Effectiveness of more than 1000mg of EPA/DHA to treat HIV/AIDS associated hypertriglyceridemia.

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when these seven were analyzed, the heterogeneity measured by I^2 of Higgins & Thompson[22] dropped to 0%. The results of each study, their respective intervals of confidence (IC) of 95% and the summary measure are shown in Graphic 3. The reduction of combined averages through random effects was -114.15 mg/dL

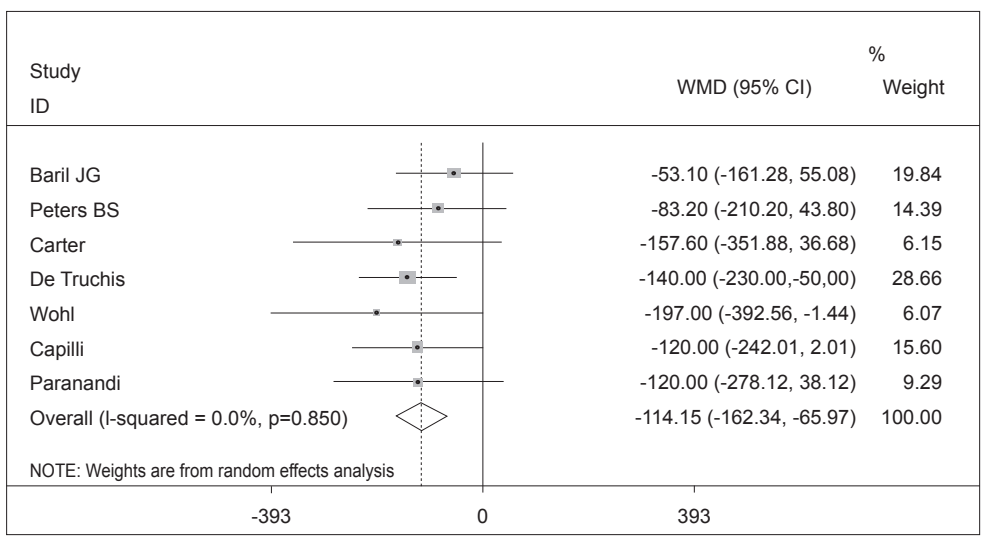
(IC from -162.34 to -65.97; p = 0.00), which can be interpreted as presence of significant reduction of triglycerides of the group with initial serum triglyceride above 200 mg/dL.

Discussion

This meta-analysis with nine studies indicated a statistically significant reduction of serum triglycerides in the Omega 3 (EPA/DHA) group when compared to control group. Similar results to the encountered in the meta-analysis of Oliveira e Stradling[12,13]. The poor result of the triglycerides reduction in the present study can be explained by the inclusion of new clinical trials[16-18] with specific characteristics discussed next. The heterogeneity encountered was considered moderate according to Higgins &Thompson[22]. Two analysis of the subgroup were conducted, the first excluding the studies that used under 1000 mg EPA/DHA day[15,16] dosages and the second, excluding the studies with initial triglycerides under 200 mg/dL[16,29]; in both studies, the heterogeneity was 0%.

Studies of the overall population show that there is a relation between levels of triglycerides and the percentage of reduction. Individuals with higher triglycerides have major percent of reduction of the EPA/DHA dosage used[32]. Balk et al.[33] in a systematic review with meta-analysis verified that each raise of 1 g/d of fish oil was associated to the reduction of triglycerides levels of approximately 8 mg/dL. Additionally, each raise of 10 mg/dL in the initial levels of triglycerides is associated to a decline of 1,6 mg/dL of triglycerides after consumption of fish oil. The degree of TG reduction would be contingent, therefore, on the initial levels of triglycerides and the dose of EPA/DHA used[14].

There was no uniformity across clinical trials in the dosage of the supplement used, with a variation of 900 to 4000 mg/day of EPA/DHA. Only two clinical trials used values below 1000mg of EPA/DHA[15,16] and presented different results. Oliveira et al.[16] did not find significant reduction when compared to the control group while in the study of Baril et al.[15] the reduction was substantial. The difference among these studies is most likely in the initial levels of triglycerides: Oliveira, under 200m/dL, and Baril, above 400mg/dL, which is the justification of Baril's study best results.



Graphic 3. Effectiveness of Omega 3 to treat HIV/AIDS associated hypertriglyceridemia in patients with triglycerides over 200 mg/dL d.

In the present study the results were clearly better when the EPA/DHA was more than 1000mg and triglycerides was over than 200 mg/dL. This becomes clear when look at the summary measured: -77,55 (-121,85 to -33,25) all group; -101,56 (-145,76 to -57,37) >1000 mg EPA/DHA; -144,15 (-162,34 to -65,97) >200 mg/dL of triglycerides.

Other studies that also adopted the same dosage of EPA/DHA[18,26,29] and that had different initial levels of TG, also presented different results. The reduction was commensurate to the initial levels of triglycerides. The higher TG, major reduction is encountered (Peters et al.[26] > 400 mg/dL, Paranandi et al.[18] >200 mg/dL and Thusgaard et al.[29] < 200 mg/dL)

Our study has limitations, due to the reduced number of studies included, different dosages of Omega 3, difference of interventions associated with concomitant use of diets, use of hypolimiants, further to initial TG levels and differences of TARV regimen. Among them, it is possible to single out the absence of non-published studies, the impossibility of evaluating the existence of bias of publication due to the small number of studies included and heterogeneity.

The recommendations for the treatment of dyslipidemia, including HIV-patients hypertriglyceridemia, are the same for the overall population. The guidelines of IDSA (Infectious Disease Society of America)[34] and ACTG (Adult AIDS Clinical Trial Group)[35] follow the recommendations of NCEP ATPIII[31]. EACS (European AIDS Clinical Society)[36] guidelines recommend healthy diet, work out and weight control to reduce dyslipidemia and among the drugs recommended for dyslipidemia management, it appears Omega 3 with dosage indication, Maxepa® 5g 2x/d(3000 mg EPA/DHA) and Omacor® 1g to 2g 2x/d (1680 mg to 3360 mg EPA/DHA) to reduce TG.

Publications about dyslipidemia management for HIV mention fish oil (supplement of EPA/DHA) as a safe and alternative treatment to reduce serum TG because it is well tolerated and does not present drug interactions with antiretroviral therapy[37-39].Recommended dosage vary from 2 to 9g/d and the supplements are indicated some times as fish oil, others as Omega 3 fatty acids and others as EPA/DHA[37,38,40-42].

Fish oil is a source of Omega 3 fatty acid containing EPA/DHA. And 1g of fish oil (or Omega 3) is not necessarily equal to 1 g of EPA/DHA, it will depend on the prescribed formulation. For this reason, the selection of supplement with bigger concentration of EPA/DHA is essential to reduce the quantity of required pills to get an effective result, thus improving the adherence to the treatment.

To achieve the dosage recommended by the AHA cardioprotective approximately 1g/day of EPA/DHA need to ingest ≈ 71g of salmon, 71-340 g of tuna, 57g of herring, 354 of cod daily[43]. The recommendation for the reduction of TG is 2 to 4 g/of which prevents the use of fish consumption for this purpose.

In two studies[44,45] comparing the use of Omega 3 and fibrates to reduce TG in HIV patients, the authors conclude that the reduction with fibrates is bigger, but it occurs also with Omega3 (n-3 polynsaturated fatty acids-PUFA, polyunsaturated ethyl esters of n-3 fatty acids- PEE) showing improved tolerability, and this may potentially mean an effective and safe alternative to fibrates.

In another study[46] evaluating the associated use of fish oil supplement with fenofibrate, which initially separated the patients received treatment for 8 weeks and those who did not respond to treatment, received combination therapy for 10 weeks. In the group receiving fish oil only TG was reduced by 46%, as received fenofibrate was 58% and that received combination therapy reduction was 65.5%, concluding that the fish oil alone or combined the fenofibrate is safe and significantly reduces TG levels in HIV patients with hypertriglyceridemia and that the combination therapy is effective for those who do not respond to therapy alone.

EPA/DHA dosage to reduce TG needs more trials. As there exists a relation between the initial TG and EPA/DHA dosage in the effective reduction, the following questions need to be responded: Will initial high TG respond better to a lower EPA/DHA dosage? And even why not ask whether, depending on the case, would it be interesting to attempt initially only with EPA and DHA prior to prescribing fibrate in specific cases, as we are dealing with patients using multiple medicines daily?

Conclusions

The findings of this study led to the conclusion that supplementation with EPA/DHA in 900 to 4,000 mg/day dosages reduce the serum levels of triglycerides in HIV/AIDS associated hypertriglyceridemia patients in stable use of antiretroviral therapy.

Supplementation with EPA/DHA promotes better responses in individuals with higher tri-

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glyceride and when offered in higher doses than 1000 mg/day.

Other clinical trials to attempt to determine EP/DHA dosages in different scenarios to promote the reduction of TG are necessary, considering the relation of initial TG and EPA/DHA dosage.

Collaborations

ADS Vieira worked in reading of scientific articles, data extraction, data analysis and final manuscript; GRM Silveira worked in reading some of the scientific articles, data extraction, data analysis and final manuscript.

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