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Research Article

A META-ANALYSIS OF OMEGA-6 FATTY ACIDS AND RISK OF INFLAMMATION

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ABSTRACT

Chronic inflammatory condition leading to the development of diseases like diabetes type II, Alzheimer's, rheumatoid arthritis, cardiovascular, peripheral arterial disease and others have driven investigators to find pro and anti-inflammatory role of various elements in the human body. Considering the vital role of the essential fatty acids in the functioning of the cell membrane, the authors took up the meta-analysis to determine if omega-6 essential fatty acid is associated with increase in C-reactive protein which is an inflammatory marker.

Electronic databases searched for this meta-analysis were Science Direct, Google scholar, Medline and Pubmed from 2003 to June 2016. Thirteen studies were identified for the analysis.4 of these studies involved normal individuals and 9 studies included subjects with the above-mentioned diseases. These studies involved1252 participants who were both healthy individuals as well as subjects with inflammatory diseases. Meta-analysis showed that supplementation of omega-6 doesn't change the level of CRP.(mean difference= -0.169, 95% confidence interval (0.72-1.06), P = 0.71, random-effects model).

This meta-analysis concluded that dietary omega-6 does not increase the risk of inflammation and chronic inflammatory conditions such as diabetes type II and cardiovascular diseases.

INTRODUCTION

Diet in general contains different types of fats. It contains both essential fats which need to be provided in the diet and the non-essential fats which can be synthesized in the body (Raafat, 2013). The essential fats are the polyunsaturated fats are the omega-3 and omega-6 fats (Fig.1). The presence of essential fats in the diet is crucial to the maintenance of health. The right balance between the various unsaturated fats is optimal to the prevention of disease. Saturated fats have been shown to be associated with disease conditions (Huang *et al*., 2017).

As cell is the basic unit of life, its functions directly influence homeostasis. Cell signaling, and gene expression depend upon the flexibility and dynamism of the cell membrane which in turn depends on the units and molecules of which it is made up of (Goñi, 2014).

The polyunsaturated fatty acids such as omega-6 and omega-3 fatty acids have been recognized as vital components of the cell membrane and its function (Raafat, 2013) (Goñi, 2014).

Essential fatty acids present in the diet influence the integral fatty acid content of the cell membrane composition and improve the various function of the cell membrane (Edel *et al*., 2008) (Yary *et al*., 2016b). Foods which contain these essential fatty acids are fish oil and vegetables oils like corn oil, walnut oil and flax seed oil, sunflower oil, soybean oil and safflower oil (Edel *et al*., 2008) (Raafat, 2013).

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Normal levels of omega-3 and omega-6 are associated with decreased risk of chronic diseases like diabetes, heart disease, hypertension, cancer and other chronic diseases. The structural difference between the main two essential fatty acids is the presence of double bonds at different positions on the carbon atom chain (Fig.2) (Hall, Shahrokhi, & Jeschke, 2012).

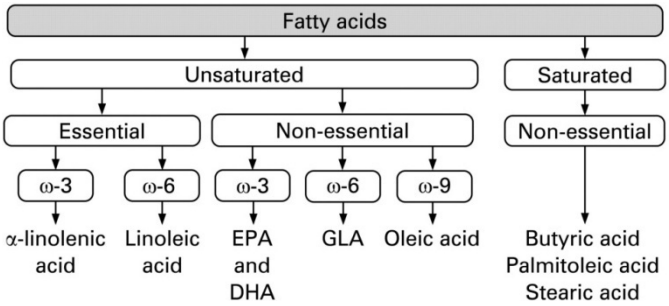

Fig1 Classification of fatty acids; DHA=docosahexaenoic acid, EPA=eicosapentaenoic acid, GLA=gamma linolenic acid.

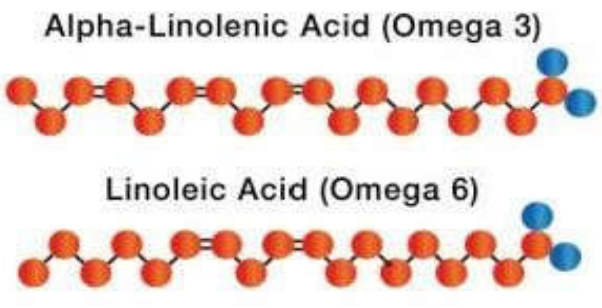

Fig 2 Structural representation of omega-3 and omega-6 fatty acids.

Omega-3 fatty acids have been considered as anti-inflammatory while omega-6 fatty acids are evidenced to be pro inflammatory (Adam *et al*., 2003)(Xu *et al*., 2016). Pro-inflammatory substances like leukotrienes and prostaglandins are formed from omega-6 fatty acids (Hussein, 2013)(Smedman, Basu, Jovinge, Fredrikson, & Vessby, 2017) (Fig3).

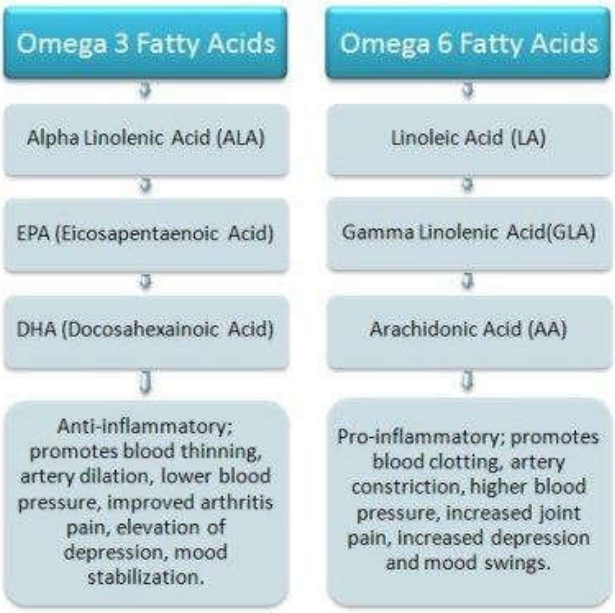

Fig 3 Basic metabolic pathway for omega-3 and omega-6, leading to anti-inflammatory and pro-inflammatory products respectively.

A balance between the functions and quantities of the essential acids can be achieved by the right ratio of the same in the diet. Being healthy has been associated with a balanced diet of omega-3 and omega-6 fatty acids (Mirmiran *et al*., 2012).
Two human studies have evidenced no association between omega-6 and inflammation (Farvid *et al*., 2014) (Yary *et al*, 2016).

The above-mentioned reasons warranted a meta-analysis, which was taken up by the authors.

MATERIALS AND METHODS

Literature Search

Electronic databases searched were Science Direct, Google scholar, Medline and Pubmed from 2003 to June 2016. The following key words were searched for in the electronic databases: omega-3 fatty acid, omega-6 fatty acid along with C-reactive protein, tumor necrosis factor alpha, interleukin 6, and inflammation. Reference lists of retrieved systematic reviews, meta-analyses and articles, were checked for additional relevant trials.

Study Selection

Thirteen randomized controlled trials with either crossover or parallel design with a total of 1252 subjects were involved in this meta-analysis.

Table 1 Enrolled Studies

Study name	Year	Sample size	Mean age	Disease status	Omega 6	Control	Mean CRP hs-CRP (mg/L)		Study Designe
Faxen Irving *et al*	2009	174	72.9± 8.6	Alzheimer's disease	1g of corn oil	Fish oil	0.8 (0.5–1.5	0.8 (0.4–2.1)	double-blind randomized placebo-controlled study=6 mon
Rhee and Brunt	2011	9	54.7 ± 6.6	obese	ground flaxseed (2.5 g/d) omega-6	placebo	C7.2±5.5	T3.9±0.9	a randomized crossover design=12 weeks (no change in inflammatory risk)
Adam *et al*	2003	68	58.0±12.5	rheumatoid arthritis	12.7 g/d omega-6	placebo	2.2±2.5	1.6±1.5	double-blind crossover study= 8 months
Kaul *et al*	2008	86	34.98 ±1.73	healthy	Flaxseed oil 1.19 g/d Omega-6	placebo	5.89±1.5	2.95±7.3	double blinded, placebo controlled, clinical trial. a 12 week
Barbosa *et al*	2003	9	40± 11	ulcerative colitis	4.5 g/day Soy oil	Fish oil	9.2± 5.6	2.4±1.0	randomized crossover design=2 months
Smedman *et al*	2004	53	47·8±10.1	healthy	conjugated linoleic acid 4·2g CLA/d	olive oil	1·24	4·95	a randomised, double-blind, placebo controlled study = 3 months
Faxen Irving *et al*	2009	89	72.6± 9	Alzheimer's disease	0.6 g LA Corn oil	Fish oil	0.8 (0.4–1.9)	0.6 (0.5–2.0)	Randomized, double-blind, placebo-controlled trial= 6 months
Mackay *et al*	2012	77	68.5	Peripheral arterial disease	Palm and soybean oils (80:20)	Fish oil	2.58 (1.51, 4.12)	1.70 (0.79, 3.97)	a randomised cross-over trial = 6 week
Chiang *et al*	2012	25	33 (23–65)	healthy	walnuts 42.5 g	placebo	2.32	2.22	randomized, controlled, single-blind, crossover trial=12 weeks
Malekshahi *et al*	2012	84	52.96 ± 10.72	type 2 diabetes	High Omega 6 sunflower oil 2.100 mg	Fish oil	20.35± 24.19	18.1± 11. 3	Randomized, double-blind, placebo-controlled trial= 8W
Pooya *et al*	2010	41	52.7 ± 10.65	type 2 diabetes	High Omega 6 sunflower oil2.100 mg	Fish oil	2.4±8 0.23	3.80 ±0.17	Randomized, double-blind, placebo-controlled trial= 2 mounth
Saifullah *et al*	2007	23	57± 14	Hemodialysis	High Omega 6 corn oil. 543 mg	Fish oil	10.5 ±12.7	20.4± ±±16.8	Randomized, double-blind, placebo-controlled trial=8 W
Skulas *et al*	2011	26	44.3 ± 6 9.8	hypertriglyceridemia	corn oil	placebo	1.26±0.83	1.45 ±0.2	Crossover study

C= intervention in control group T= intervention in treatment group

Data Extraction and Analyses

The analysis includes 13 studies, in each study, there are two groups; treated group and placebo or control group. The treated group was given omega-6 and the control group was given the placebo. Then the effect size (differences in mean of the blood CRP in both groups) were calculated.

Data extracted from each study were: name of author's, publication year, sample size, participants age ,status of participiants , trail design (parallel design or crossover design), duration of follow-up, description of omega-6 intervention and respective placebo; Data of fasting blood level of CRP (All studies expressed data as mean ± standard deviations or median, post-intervention differences in mean of both treated and control groups. Data were analyzed using the comprehensive meta-analysis program.

RESULTS

Enrolled Studies

The selected studies are displayed in table 1.Thirteen studies involving 1252 participants included healthy individuals and patients with different disease as subjects, 4 studies involved healthy individuals as subjects, and other 9 studies involved patients with different disease such astype 2 diabetes, rheumatoid arthritis alzheimer's disease, peripheral arterial disease,ulcerative colitis as subjects. Twelve studies including 1199 participants used omega-6 PUFAs supplementation (vegetable oil rich in omega-6) as active treatment, and only one study including 53 independent comparisons used omega-6 from conjugated linoleic acid as active treatment.

Effect of Omega-6 fatty acids Supplementation on CRP level

In most studies meta-analysis showed that supplementation of omega-6 doesn't significantly change the level of CRP. According to the forest plot (mean difference = -0.169 mg/L, 95% confidence interval(0.72-1.06), P = 0.71, random-effects model). The effect size= -0.169 that mean the omega-6 decrease the level of CRP by a mean of 0.169 mg/ L. The confidence interval is 0.72 to1.06 mg/ L that means the mean difference at least 0.72 mg/ L and as much as 1.06 mg/ L.

Since this range includes zero line of forest plot (Figure1), the difference is not statically significant. And the p-value of the summary of the effect size is >0.001 which is not statically significant.

DISCUSSION

Omega-6 essential polyunsaturated fatty acid is protective against certain diseases like type II diabetes, hypertention, rheumatoid Arthritis and cardiovascular conditions (Farvid *et al*., 2014) (Yary *et al*, 2016b). The protective effect of omega-6 against these chronic diseases may attributed to its positive effects on the health of the cell membrane (Raafat, 2013). Supplementation with omega-6 is beneficial as it has shown in a study to reduce the risk of developing cardiovascular disease by 14% (Farvid *et al*., 2014). 46% decrease in the development of diabetes type II was also reported by a study (Yary *et al*, 2016b). No relationship between Inflammation and omega-6 was established (Yary *et al*, 2016b). Different studies, in general, suggest an overall benefit of omega-6 fatty acids supplement onseveral inflamatory conditions riskand no significant effect on cancer (Gillman *et al*, 1997) (P L Zock and M B Katan, 1998).

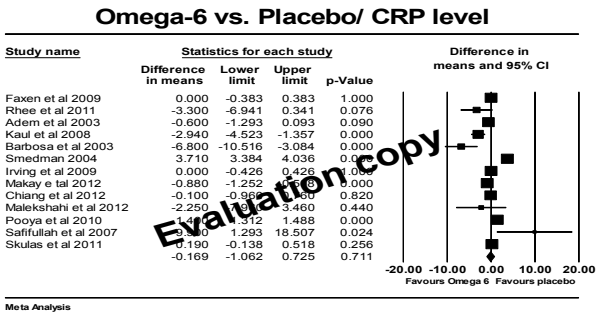

Figure1.Pooled effect size of omega-6 supplementation on blood C- reactive protein (mg/L) levels. Forest plot showing statistic of each study including mean differences (MD) with 95% confidence intervals. For each study, each square represents the effect size. Each horizontal line represents the 95% confidence intervals of these effects. The size of the square represents the weight of the study. Vertical line is the line of no effect. The diamond at the end of the graph reflects the meta-analytic summary of all studies.

Studies have drawn attention to the ratio of omega-3 and omega-6 fatty acids. More omega-6 and less omega-3 is the content of the present-day diet in general (Mirmiran *et al*., 2012) (Simopoulos *et al*., 2016). This markedly unbalanced ratio is implicated in the development of inflammation and subsequently the various diseases (Mirmiran *et al*., 2012).

The meta-analysis did not show that there is an increase in the inflammatory marker (C-reactive protien) due to omega-6 spplementation in healthy as well as diseased individuals.

Study Limitation

Studies varied with respect to trail design, e.g., amount of vegetable oil used, length of intervention, number of participants. In addition, in all trials, the type of oils (hydrogenated,partial hydrogenated or clod pressed) that were used as a source of omega-6 is not mentioned.

CONCLUSION AND RECOMMENDATIONS

This meta-analysis concludes that dietary omega-6 does not increase the risk of inflammation and chronic inflammatory conditions such as diabetes type II and cardiovascular diseases. Further studies involving determination of the omega-6 and omega-3 ratios in the blood and in the cell membrane may give clearer picture of the roles of these fatty acids in the maintenance of normal cell membrane and cell function. These studies can provide better definitive guidelines about supplementation and prevention of disease. Basic science investigations at the cellular and molecular levels are highly warranted. Further long term studies involving larger sample size may provide a basis for basic science investigations.

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