

openheart Importance of maintaining a low omega-6/omega-3 ratio for reducing inflammation

James J DiNicolantonio, James H O'Keefe

To cite: DiNicolantonio JJ, O'Keefe JH. Importance of maintaining a low omega-6/omega-3 ratio for reducing inflammation. *Open Heart* 2018;5:e000946. doi:10.1136/openhrt-2018-000946

Accepted 15 November 2018

INTRODUCTION

The consumption of seed oils high in the omega-6 polyunsaturated fat (PUFA) linoleic acid (LA) contributes to low-grade inflammation, oxidative stress, endothelial dysfunction and atherosclerosis.¹ Moreover, dietary LA significantly increases cyclooxygenase-2 (COX-2) expression in the aorta,² converting arachidonic acid (AA) to proinflammatory eicosanoids. This may explain why increasing LA intake can actually lower AA levels due to an increased breakdown into harmful proinflammatory metabolites. Additionally, there is an AA-independent pathway of inflammation promoted by the intake of omega-6 seed oils such as increased production of oxidised linoleic acid metabolites (OXLAMs) and proinflammatory LA CYP-eicosanoids.³⁻⁵ OXLAMs formed from LA activate NF-kB and increase proinflammatory cytokines, endothelial adhesion molecules, as well as chemokines, all of which are paramount in the formation of atherosclerosis.⁵⁻⁸ LA also induces an inflammatory environment in endothelial cells that may increase the risk of coronary heart disease (CHD).⁸ OXLAMs are found at a 50-fold higher concentration in plasma than AA metabolites, suggesting that they are more consequential in CHD and other chronic diseases,^{2 3 9} and lowering dietary LA reduces OXLAMs in the body.³

By inhibiting COXs and lipoxygenases (LOXs), marine omega-3s can reduce inflammation caused by the metabolism of AA. Indeed, compared with high-oleic sunflower oil (3.5 g/day), fish oil (3.5 g/day) reduces acute phase reactants (haptoglobin precursor, haemopexin, alpha-1-antitrypsin precursor and serum amyloid P component). The authors concluded, 'The alterations in serum proteins... imply that fish oil activates anti-inflammatory mechanisms believed to impede the early onset of CHD'.¹⁰ In human atherosclerotic lesions, as the atherosclerotic

lesion becomes more advanced, the ratio between oxidised LA and unoxidised LA increases.¹¹ Moreover, rats fed LA have a significant increase in tumour necrosis factor (TNF)-alpha (p<0.05) in plasma, and higher levels of vascular cell adhesion molecule-1 (VCAM-1), intracellular adhesion molecule-1 (ICAM-1) and NF-kB in aortas. The authors concluded that '...our results demonstrated that an excess of LA is more efficient to activate endothelial molecular process than an excess of saturated fatty acids'.²

Two phase III, double-blind studies randomised hypertriglyceridemic patients to marine omega-3s (icosapent ethyl trade name Vascepa 4 g/day, Vascepa 2 g/day or placebo).¹² These included patients on statins with residual high TG ≥ 200 mg/dL < 500 mg/dL (ANCHOR) or very high TG with or without statin (≥ 500 to < 2000 mg/dL (MARINE)). The authors concluded, 'Compared with placebo, icosapent ethyl 4 g/day significantly decreased oxidized-low density lipoprotein (Ox-LDL) (13%, p<0.001, ANCHOR), Lp-PLA2 (14%, p<0.001, MARINE; 19%, p<0.001, ANCHOR), and high-sensitivity c-reactive protein (hsCRP) levels (36%, p<0.01, MARINE; 22%, p<0.001, ANCHOR)'.¹² The benefits regarding a reduction in ox-LDL was not found with 2 g of Vascepa/day, suggesting that 4 g of Vascepa (3.4 g of eicosapentaenoic acid (EPA) as ethyl esters) may be ideal for reducing ox-LDL.¹² Furthermore, DHA alone (at 3 g/day) has been found to reduce inflammation (interleukin (IL)-6, hsCRP and granulocyte monocyte-colony stimulating factor) in men with hypertriglyceridaemia after 3 months of use and to increase the anti-inflammatory matrix-metalloproteinase-2.¹³ Thus, it appears that both EPA and docosahexaenoic acid (DHA) have anti-inflammatory benefits. The recent announcement of results from the Reduction of Cardiovascular Events with EPA Intervention Trial (REDUCE-IT) study,



© Author(s) (or their employer(s)) 2018. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

Saint Luke's Mid America Heart Institute, Kansas, Missouri, USA

Correspondence to

Dr James J DiNicolantonio; jdinicol@gmail.com

which found a highly significant reduction in cardiovascular events using Vascepa 4 g per day, suggests how these anti-inflammatory benefits may cause reductions in clinical endpoints.

A systematic review of 26 randomised controlled trials (RCTs) concluded, 'Dietary omega-3 fatty acids are associated with plasma biomarker levels, reflecting lower levels of inflammation and endothelial activation in cardiovascular disease and other chronic and acute diseases, including chronic renal disease, sepsis and acute pancreatitis'.¹⁴ DHA may be particularly effective for reducing cytokine-induced endothelial leucocyte adhesion molecules due to its ability to incorporate into cellular lipids.¹⁵ Moreover, DHA reduces COX-2 expression,¹⁶ which also reduces inflammatory eicosanoid production from AA.

Omega-3 PUFAs also reduces adhesion molecules (VCAM-1 and ICAM-1), chemokines (MCP-1), matrix metalloproteinases and inflammatory cytokines.¹⁷ Another meta-analysis of 18 RCTs found that supplementing with omega-3 PUFAs significantly reduces soluble intercellular adhesion molecule-1, suggesting that marine omega-3s inhibit atherosclerosis formation, whereas LA can activate vascular endothelial cells, which is a critical event in inducing atherosclerosis.^{18 19}

In a cross-sectional study, the omega-3 index (omega-3 PUFA content of red blood cells) was inversely related to inflammation (C reactive protein (CRP) and IL-6) in patients with peripheral arterial disease (PAD).²⁰ Those with a mean omega-3 index of 6.8% had the lowest log-CRP values (0.6 mg/L) compared with those with omega-3 indexes of 4.5% and 3.7% (1.4 mg/L for both). The authors suggested that fish oil in patients with PAD would likely improve inflammation, symptoms and possibly reduce the progression and severity of the disease. However, LA in red blood cells and in plasma does not correlate well with intake, whereas DHA, especially in red blood cells but also in plasma, had good correlation (EPA also had fairly good correlation with intake as well but only with red blood cell levels).²¹

The omega-3 index is an independent risk factor for CHD mortality²² and is inversely related with inflammation (CRP and IL-6) in patients with stable CAD.²³ One study found that omega-3s (around 25 oz. of fatty fish weekly plus 15 mL (one tablespoonful) of sardine oil daily) in those over 60 years of age reduces inflammation (CRP and IL-6) and improves insulin sensitivity, which may partially be due to its ability to reduce free fatty acids release by catecholamines.²⁴

Compared with 15 mL/day of safflower oil (rich in LA) consuming 15 mL of flaxseed oil (around 7 g of alpha linolenic acid (ALA)/day) for 3 months decreases CRP (38%), serum amyloid A (23.1%) and IL-6 (10.5%).²⁵ Moreover, compared with margarine rich in LA, margarine rich in ALA (total ALA intake around 6–8 g/day) significantly reduced CRP after 1 and 2 years (–0.53 mg/L and –0.56 mg/L, respectively).²⁶ Thirty grams of flaxseed flour (5 g of ALA/day) has been found to significantly reduce CRP, serum amyloid A, white cell count and

fibronectin, suggesting that flaxseed may be beneficial for suppressing chronic low-grade inflammation in obesity.²⁷

DECREASING THE OMEGA-6/3 RATIO DECREASES INFLAMMATION

Decreasing the omega-6/3 ratio seems to reduce the inflammatory response to a high-fat meal. For example, one study looked at responses in men with metabolic syndrome to an oral fat tolerance test (OFTT) by adjusting the omega-6/3 ratio. Patients ingested two high-saturated fat OFTTs (1 g fat/kg body weight) with either a high omega-6/3 ratio (~18:1) or a low omega-6/3 ratio (~3:1) and a water control in a randomised crossover design. Reducing the omega-6/3 ratio caused a lower release of the proinflammatory cytokine IL-6 at hours 6 and 8.²⁸ Additionally, Nelson and Hickey performed a study showing that an isocaloric replacement of LA with ALA for just 4 days leads to a reduction in soluble IL-6 receptor.²⁹ These studies suggest that replacing omega-6 with omega-3 reduces inflammation.

One study took mice and divided them into four groups feeding them different diets varying the omega-6/3 ratio (ie, group 1=0.29, group 2=1.43, group 3=5.00 and group 4=8). The diets were prepared with high ALA flaxseed oil or high LA safflower oil. Group 1, which was the lowest omega-6/3 ratio group, had the lowest triglyceride and low-density lipoprotein (LDL) levels and the highest high-density lipoprotein (HDL) levels. Thrombosis and atherosclerosis was also less in animals fed the low omega-6/3 diet compared with the high omega-6/3 diet. Indeed, there was a 40% reduction in atherosclerotic area with the lowest omega-6/3 ratio versus the highest omega-6/3 ratio. The authors concluded that, 'The lowest n-6/n-3 ratio tested (0.29) was the most effective in suppressing the thrombotic and atherosclerotic parameters in these double knockout (apoE-/- & LDLR-/-) mice'.³⁰ In summary, replacing omega-6 safflower oil with omega-3 linseed (flaxseed) oil reduces atherosclerosis and thrombogenesis in mice.

Another animal study fed mice different high saturated fat diets differing only in the omega-6/EPA+DHA ratio to produce either: (1) no EPA+DHA diet, (2) omega-6/3 ratios of 20:1, (3) omega-6/3 ratio of 4:1 and (4) omega-6/3 ratio of 1:1 for 32 weeks to see if any differences could be found. Mice fed the lowest omega-6/3 ratio had the lowest non-HDL (ie, atherogenic lipoproteins) and inflammation (IL-6). Mice fed lower omega-6/omega-3 ratio diets also had less macrophage cholesterol accumulation as well as less aortic atherosclerotic lesions. The lowest omega-6/3 ratio (1:1) diet led to the least atherosclerotic formation and the severity of atherosclerosis increased as the omega-6/3 ratio increased.³¹

CONCLUSION

The reddening and swelling of areas in the body generally occurs because of the release of omega-6 (AA) eicosanoids and cytokines. This happens when AA is

metabolised by cyclooxygenases (COX1 and COX2) or LOXs. Aspirin, for example, a well-known pain reliever and fever reducer, inhibits COX1 from breaking down AA, thereby preventing the inflammatory response. Non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and naproxen inhibit both COX1 and COX2 and are the most popular over-the-counter pain relievers showing just how powerful the proinflammatory metabolites are from AA. Instead of using NSAIDs to inhibit the formation of omega-6 AA metabolites, eating more EPA/DHA can provide a similar effect. Omega-3s PUFAs act to prevent chronic low-grade inflammation. Indeed, supplementing with fish oil is known to inhibit inflammatory cytokines such as TNF-alpha and IL-1 beta and proinflammatory/proaggregatory eicosanoids such as thromboxane-2 and prostaglandin E2.³² Using long-chain omega-3s to suppress low-grade inflammation may benefit numerous chronic diseases such as rheumatoid arthritis, atherosclerosis, dyslipidaemia, diabetes, obesity and heart failure.³² The consumption of omega-6 seed oils may have the opposite effect.

Contributors JJD performed the literature search and wrote the initial manuscript. JHO reviewed and edited the paper.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests JJD is author of Superfuel and The Salt Fix. JHO is Chief Medical Officer and Founder of CardioTabs, a nutraceutical company, and does have a major ownership interest in the company. CardioTabs does sell products that contain omega-3.

Patient consent Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <https://creativecommons.org/licenses/by-nc/4.0/>

REFERENCES

- Hennig B, Toborek M, McClain CJ. High-energy diets, fatty acids and endothelial cell function: implications for atherosclerosis. *J Am Coll Nutr* 2001;20:97–105.
- Marchix J, Choque B, Kouba M, et al. Excessive dietary linoleic acid induces proinflammatory markers in rats. *J Nutr Biochem* 2015;26:1434–41.
- Ramsden CE, Ringel A, Feldstein AE, et al. Lowering dietary linoleic acid reduces bioactive oxidized linoleic acid metabolites in humans. *Prostaglandins Leukot Essent Fatty Acids* 2012;87:135–41.
- Reinaud O, Delaforge M, Boucher JL, et al. Oxidative metabolism of linoleic acid by human leukocytes. *Biochem Biophys Res Commun* 1989;161:883–91.
- Choque B, Catheline D, Rioux V, et al. Linoleic acid: between doubts and certainties. *Biochimie* 2014;96:14–21.
- Friedrichs B, Toborek M, Hennig B, et al. 13-HPODE and 13-HODE modulate cytokine-induced expression of endothelial cell adhesion molecules differently. *Biofactors* 1999;9:61–72.
- Fei J, Cook C, Gillespie M, et al. Atherogenic ω -6 lipids modulate PPAR- EGR-1 Crosstalk in vascular cells. *PPAR Res* 2011;2011:1–11.
- Toborek M, Lee YW, Garrido R, et al. Unsaturated fatty acids selectively induce an inflammatory environment in human endothelial cells. *Am J Clin Nutr* 2002;75:119–25.
- Yoshida Y, Yoshikawa A, Kinumi T, et al. Hydroxyoctadecadienoic acid and oxidatively modified peroxiredoxins in the blood of Alzheimer's disease patients and their potential as biomarkers. *Neurobiol Aging* 2009;30:174–85.
- de Roos B, Geelen A, Ross K, et al. Identification of potential serum biomarkers of inflammation and lipid modulation that are altered by fish oil supplementation in healthy volunteers. *Proteomics* 2008;8:1965–74.
- Kühn H, Heydeck D, Hugou I, et al. In vivo action of 15-lipoxygenase in early stages of human atherogenesis. *J Clin Invest* 1997;99:888–93.
- Bays HE, Ballantyne CM, Braeckman RA, et al. Icosapent ethyl, a pure ethyl ester of eicosapentaenoic acid: effects on circulating markers of inflammation from the MARINE and ANCHOR studies. *Am J Cardiovasc Drugs* 2013;13:37–46.
- Kelley DS, Siegel D, Fedor DM, et al. DHA supplementation decreases serum C-reactive protein and other markers of inflammation in hypertriglyceridemic men. *J Nutr* 2009;139:495–501.
- Rangel-Huerta OD, Aguilera CM, Mesa MD, et al. Omega-3 long-chain polyunsaturated fatty acids supplementation on inflammatory biomarkers: a systematic review of randomised clinical trials. *Br J Nutr* 2012;107:S159–70.
- De Caterina R, Cybulsky MA, Clinton SK, et al. Omega-3 fatty acids and endothelial leukocyte adhesion molecules. *Prostaglandins Leukot Essent Fatty Acids* 1995;52:191–5.
- Massaro M, Habib A, Lubrano L, et al. The omega-3 fatty acid docosahexaenoate attenuates endothelial cyclooxygenase-2 induction through both NADP(H) oxidase and PKC epsilon inhibition. *Proc Natl Acad Sci U S A* 2006;103:15184–9.
- The Island Where People Forget to Die. Available from: <https://www.nytimes.com/2012/10/28/magazine/the-island-where-people-forget-to-die.html> [Accessed 9 Aug 2018].
- Hennig B, Meerarani P, Ramadass P, et al. Fatty acid-mediated activation of vascular endothelial cells. *Metabolism* 2000;49:1006–13.
- Toborek M, Hennig B. The role of linoleic acid in endothelial cell gene expression. Relationship to atherosclerosis. *Subcell Biochem* 1998;30:415–36.
- Grenon SM, Conte MS, Nosova E, et al. Association between n-3 polyunsaturated fatty acid content of red blood cells and inflammatory biomarkers in patients with peripheral artery disease. *J Vasc Surg* 2013;58:1283–90.
- Sun Q, Ma J, Campos H, et al. Comparison between plasma and erythrocyte fatty acid content as biomarkers of fatty acid intake in US women. *Am J Clin Nutr* 2007;86:74–81.
- Harris WS. The omega-3 index as a risk factor for coronary heart disease. *Am J Clin Nutr* 2008;87:1997S–2002.
- Farzaneh-Far R, Harris WS, Garg S, et al. Inverse association of erythrocyte n-3 fatty acid levels with inflammatory biomarkers in patients with stable coronary artery disease: The Heart and Soul Study. *Atherosclerosis* 2009;205:538–43.
- Tsitouras PD, Gucciardo F, Salbe AD, et al. High omega-3 fat intake improves insulin sensitivity and reduces CRP and IL6, but does not affect other endocrine axes in healthy older adults. *Horm Metab Res* 2008;40:199–205.
- Rallidis LS, Paschos G, Liakos GK, et al. Dietary alpha-linolenic acid decreases C-reactive protein, serum amyloid A and interleukin-6 in dyslipidaemic patients. *Atherosclerosis* 2003;167:237–42.
- Bemelmans WJ, Lefrandt JD, Feskens EJ, et al. Increased alpha-linolenic acid intake lowers C-reactive protein, but has no effect on markers of atherosclerosis. *Eur J Clin Nutr* 2004;58:1083–9.
- Faintuch J, Horie LM, Barbeiro HV, et al. Systemic inflammation in morbidly obese subjects: response to oral supplementation with alpha-linolenic acid. *Obes Surg* 2007;17:341–7.
- Tulk HM, Robinson LE. Modifying the n-6/n-3 polyunsaturated fatty acid ratio of a high-saturated fat challenge does not acutely attenuate postprandial changes in inflammatory markers in men with metabolic syndrome. *Metabolism* 2009;58:1709–16.
- Nelson TL, Hickey MS. Acute changes in dietary omega-3 fatty acid intake lowers soluble interleukin-6 receptor in healthy adult normal weight and overweight males. *Cytokine* 2004;26:195–201.
- Yamashita T, Oda E, Sano T, et al. Varying the ratio of dietary n-6/n-3 polyunsaturated fatty acid alters the tendency to thrombosis and progress of atherosclerosis in apoE-/- LDLR-/- double knockout mouse. *Thromb Res* 2005;116:393–401.
- Wang S, Wu D, Matthan NR, et al. Reduction in dietary omega-6 polyunsaturated fatty acids: eicosapentaenoic acid plus docosahexaenoic acid ratio minimizes atherosclerotic lesion formation and inflammatory response in the LDL receptor null mouse. *Atherosclerosis* 2009;204:147–55.
- Barceló-Coblijn G, Murphy EJ. Alpha-linolenic acid and its conversion to longer chain n-3 fatty acids: benefits for human health



and a role in maintaining tissue n-3 fatty acid levels. *Prog Lipid Res*

2009;48:355–74.