openheart

Importance of maintaining a low omega-6/omega-3 ratio for reducing platelet aggregation, coagulation and thrombosis

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To cite: DiNicolantonio JJ, OKeefe J. Importance of maintaining a low omega-6/omega-3 ratio for reducing platelet aggregation, coagulation and thrombosis. *Open Heart* 2019;**6**:e001011. doi:10.1136/openhrt-2019-001011

Accepted 14 April 2019

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The idea that long-chain marine omega-3s can prevent cardiovascular disease is decades old. This idea began with the Greenland Inuit who were noted to have a lower risk of cardiovascular disease.[1] Indeed, the Inuit, with their high intake of long-chain omega-3s, have been noted to have a lower platelet count, reduced platelet reactivity, prolonged bleeding times and a lower ratio of proaggregatory thromboxanes versus anti-aggregatory prostacyclins.[2] And it has been known for a long time that marine omega-3s (from salmon, mackerel, fish oil or cod liver oil) inhibit platelet aggregation.

OMEGA-3S REDUCE PLATELET AGGREGATION, COAGULATION AND THROMBOSIS

Clinical studies in humans clearly show that marine omega-3s provide antiplatelet effects. Indeed, a meta-analysis of 15 randomised controlled trials (RCT) in humans has confirmed that omega-3 polyunsaturated fatty acids (PUFA) inhibit platelet aggregation.[3] Marine omega-3 PUFAs also may help overcome aspirin resistance.[4] In healthy borderline overweight men, 3 g of omega-3 PUFAs for 4 weeks lowered fibrinogen, thrombin and factor V levels; these benefits occurred mainly in those with high fibrinogen carrying alpha-chain fibrinogen polymorphism.[5]

Marine omega-3s also have the ability to reduce von Willebrand factor (vWF; a platelet activator factor), whole blood viscosity, and can improve red blood cell flexibility (deformability).[6 7] In a 5-week double-blind placebo-controlled study in 30 healthy subjects, 2.52 g/day of omega-3 PUFAs as compared with 1.26 g/day, significantly decreased plasma viscosity, red blood cell rigidity and systolic blood pressure.[8] Thus, higher doses of marine omega-3 seem to be more effective antithrombotic benefits.

One study in healthy adults found that fish oil (providing 6 g of eicosapentaenoic acid (EPA)/day), but not vegetable oil, reduced platelet adhesiveness.[9] In another study, supplementation with 3.6 g of omega-3 PUFA from fish oil reduced platelet aggregation, whereas 25 g of soy lecithin (providing 1.5 g omega-6, 0.5 g omega-3) increased platelet reactivity; no effect was found in the control group.[10] The omega-6/omega-3 ratio in platelets is also positively correlated with platelet adhesion at rest and after ADP and thrombin platelet stimulation. Another study found that plasminogen activator inhibitor-1 (PAI-1, an inhibitor of fibrinolysis) can be lowered in those consuming fish oil, suggesting a decreased risk of thrombosis.[11]

In general, approximately 2–4 g of EPA/docosahexaenoic acid (DHA) per day is needed to provide the full antiatherosclerotic, anti-inflammatory and antiplatelet benefits.[12] Even plant omega-3s seem to have some benefit in this regard, whereas omega-6 may have a detrimental effect. Indeed, on a diet high in monounsaturated fatty acids (MUFA), as the omega-6 linoleic acid (LA)/omega-3 alpha linolenic acid (ALA) ratio decreases, platelet aggregation decreases.[13] In vitro platelet aggregation to both ADP and collagen is even increased after sunflower and rapeseed oil compared with a diet enriched in milk fat.[14] This suggests that even compared with saturated fat, a diet high in omega-6 PUFA may actually increase platelet aggregation.

In 24 healthy young males, a Mediterranean diet has been found to reduce the thrombotic state (decreased plasma vWF, tissue factor pathway inhibitor and tissue PAI-1).[15] Oleic acid may provide similar, but slightly less antiplatelet effects as long-chain marine omega-3s since the omega-9 fatty acid eicosatrienoic acid has also been found to reduce

the production of thromboxane-B2 (TXB2), which is the inactivated metabolite of TXA2 (a platelet activator).[16] Moreover, in another study, TXB2 production in platelets was reduced with olive oil supplementation but not with a corn oil-enriched diet.[16] Animal studies confirm a reduction in TXB2 with the use of olive oil, an effect which is greater than that found with sunflower oil.[17] Another study found a reduction in thromboxane production (urinary excretion of the TXB2 metabolite 11-dehydro-TXB2) with saturated fat and MUFA versus omega-6 PUFA.[18] A Mediterranean diet high in MUFA reduces vWF (which is derived from the endothelium and is important in the coagulation process during a platelet thrombus) and PAI-1.[15 19]

The type of long-chain marine omega-3 may also affect the antiplatelet effects of marine omega-3s. Indeed, platelet aggregation in response to collagen is reduced in just 6 days after pure EPA consumption but platelet response to ADP is not reduced until after at least 4 weeks of intake; however, the inhibition of platelet aggregation with DHA (6 g/day) to both stimuli occurs in just 6 days.[20] Thus, both EPA and DHA inhibit platelet aggregation; however, DHA has a faster onset of action in regard to inhibiting ADP-induced platelet aggregation.

Both EPA and DHA get incorporated into platelet phospholipids at the expense of arachidonic acid (AA), which may help reduce platelet aggregation via a reduction in AA-derived platelet-aggregating/procoagulant metabolites. Additionally, EPA competes with AA for cyclo-oxygenase reducing its action on AA. Thus, EPA both directly and indirectly reduces the formation of the AA proaggregatory metabolite TXA2.[20] EPA/DHA also gets incorporated into neutrophils and red blood cells at the expense of both LA and AA. The incorporation of omega-3s in red blood cells seems to decrease whole blood viscosity and increase red blood cell flexibility thus likely reducing the risk of thrombosis.[6 7]

Daily supplementation with 3 g of EPA/DHA for 12 weeks, and especially after 18 weeks, inhibits tissue factor activity in adherent monocytes (a catalyst in the coagulation cascade); this benefit also occurs after 24 weeks in those with hypertriglyceridaemia.[21] Thus, the antithrombotic effects of omega-3s in clinical studies may need to be tested for a minimum of 18 weeks in healthy patients and even longer (for 24 weeks) in those with hypertriglyceridaemia.

One study in healthy young men found that both lean meat and fish have antithrombotic effects although some prothrombotic effects (such as an increase in PAI-1) were also noted with increased fish intake.[22] A decrease in platelet aggregation but an increase in PAI-1 has sometimes been noted with fish oil supplementation. This increase in PAI-1 may actually occur to naturally counteract any excessive inhibition in the coagulation cascade, which is why supplementing with marine omega-3s is not associated with a significant increase in major or clinically significant bleeds. And considering that marine omega-3s consistently lower the risk of thrombotic events,[12 23] there does not appear to be increased coagulation but a decrease. Interestingly, supplementing the diet with olive oil or consuming fish on top of a MUFA-enriched Mediterranean diet has been found to decrease PAI-1.[15 24]

One double-blind placebo-controlled trial in 59 patients with hypertension with type 2 diabetes compared 4 g/day of EPA, 4 g/day of DHA or 4 g/day of olive oil ('placebo') for 6 weeks.[25] DHA, but not EPA, significantly reduced collagen aggregation and TXB2 versus placebo (p=0.05 and p=0.03, respectively). The authors concluded, 'Highly purified DHA may be a more effective anti-thrombotic agent than EPA.' Thus, supplementing patients with type 2 diabetes with 4 g of DHA per day may be particularly effective for quickly reducing platelet aggregation, reversing impaired fibrinolysis and improving endothelial dysfunction.[25] Even so, the REDUCE-IT study found a significant reduction in cardiovascular events in high-risk patients using 4 g of EPA per day.[26]

The endothelial production of nitric oxide, prostacyclin and tissue-plasminogen activator is very important for preventing platelet aggregation and acute cardiovascular events.[27] By damaging the endothelium, consuming isolated sources of LA may actually induce a hypercoagulable state, whereas fish oil has been shown to improve endothelial function[28] and enhance fibrinolytic activity.[29] DHA, but not EPA, has been found to improve endothelial function, which may be why DHA has been found to have better antihypertensive effects.[30] Importantly, in healthy patients, a DHA dose of 6 g/day may be required to significantly reduce platelet aggregation[31 32] as 1.62 and 1.68 g of DHA/day have been found ineffective in this regard.[33 34]

Supplementing the diet with 500 g (about 17.5 oz) of oily fish per week for 4 weeks significantly reduces platelet-monocyte aggregates by 35% versus control, which reverted back to baseline values 4 weeks after discontinuation.[35] Platelet-monocyte aggregates may promote atherosclerosis and induce inflammatory cytokine, chemokine and adhesion molecule expression. In fact, the authors concluded, 'Our results suggest that reduced platelet activation could represent an important mechanism through which dietary fish confer their putative cardiovascular benefits.'[35] EPA has also been found to reduce P-selectin, oxidised low-density lipoprotein (LDL) antibodies and glycoprotein IIb/IIIa expression on platelets.[36] Another report found that 6.6 g of omega-3 PUFA reduces serum P-selectin expression suggesting a decrease in platelet activation.[37] The authors noted, 'Most previous studies assessing the effects of fish oils on platelet function have used older techniques with limited reproducibility and physiological relevance.'[37]

MARINE OMEGA-3S DO NOT INCREASE THE RISK OF BLEEDS, AND MAY REDUCE THEM

Regarding safety and bleeding with omega-3s, Dr William Harris summarised the evidence nicely in a 2007 publication. The paper included patients undergoing major

surgeries (2 studies were in coronary artery bypass graft patients, 2 studies in carotid endarterectomy and 15 studies in femoral artery catheterisation) and Dr Harris concluded, 'In these studies, the risk for clinically significant bleeding was virtually nonexistent.'[38] He also cites a study showing that giving pregnant women 2.7 g/day of omega-3 does not increase blood loss at delivery.[39] Dr Harris concluded, 'Thus, the experience has been virtually unanimous: omega-3 fatty acid supplements do not increase the risk for clinically significant bleeding, even in patients also being treated with antiplatelet or antithrombotic medications.' Dr Harris considered the level of evidence supporting this notion as the highest we have in medicine (level of evidence A, from well-designed RCTs).[38]

A recent randomised trial further contradicts the long-held clinical assumption that omega-3 fatty acids increase risk of bleeding during and/or surgery. In the OPERA study, 1516 patients scheduled for cardiac surgery were randomly assigned to matching placebo or fish oil (EPA+DHA; 8–10 g over 2–5 days before surgery, then 2 g/day on the morning of the surgery until discharge). The omega-3 supplementation did not increase the risk of perioperative bleeding and, unexpectedly, significantly reduced the number of units of blood transfused.[40] The authors concluded, 'Higher achieved omega-3 PUFA levels were associated with lower risk of bleeding.'[40]

A HIGH OMEGA-6/OMEGA-3 RATIO INCREASES PLATELET AGGREGATION

Compared with saturated fat plus trans fat, a meta-analysis of RCTs found an increased risk of all-cause mortality, coronary heart disease mortality and cardiovascular events with omega-6 industrial seed oils.[41] This may have to do with the metabolites of omega-6 PUFAs being largely proinflammatory/proaggregatory.[42] Indeed, omega-3 and omega-6 PUFAs are supposed to balance each other out when they are consumed in the diet at a ratio of around 1 to 1.[43] However, the increase in our omega-6/omega-3 ratio has shifted the balance into a proinflammatory/proaggregatory state. Despite LA's ability to lower LDL levels, it can increase LDL susceptibility to oxidation and lipid peroxidation levels[44 45] and hence may actually increase the risk of coronary artery disease[46] as the peroxidation of LA in LDL is thought to be one of the earliest promoters of atherosclerosis. More importantly, oxidised metabolites of LA can increase thrombosis and vasoconstriction by reducing prostacyclin in the vascular wall and increasing TXA2.[47] Moreover, consuming LA from industrial seed oils may even increase the susceptibility to fatal arrhythmias.[48]

One cross-over study compared a low-erucic acid rapeseed oil (canola oil) versus high-oleic acid sunflower oil to see if there were any differences on platelet aggregation by using oils with a high versus a low LA/ALA ratio. The canola oil provided an omega-6/omega-3 ratio of just 2.8, whereas those given the high-oleic sunflower oil were provided with an omega-6/omega-3 ratio of 28. In those provided a high omega-6/omega-3 ratio using the high-oleic sunflower oil there was an increase in platelet aggregation versus the low omega-6/omega-3 canola oil group. Platelet aggregation was also enhanced in the high-oleic sunflower oil group versus the baseline habitual diet. Thus, even a high-oleic acid omega-6 industrial seed oil may increase cardiovascular risk. The authors noted that as the omega-6 (LA) to omega-3 (ALA) ratio increased so did platelet aggregation.[13]

In summary, the long-chain omega-3 PUFAs EPA and DHA have antiplatelet effects, but do not increase the risk of clinically significant bleeds and may even reduce the risk of bleeding in the surgical setting, whereas the omega-6 PUFA LA has little effect on reducing platelet aggregation and in some instances may even increase platelet activation. Omega-6 industrial seed oils, as well as suboptimal intakes of marine omega-3s, may increase the risk of thrombotic cardiovascular events. This has been suggested in numerous randomised clinical studies in humans.

Contributors All authors contributed to the final manuscript.

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests JJDN is the author of The Salt Fix and Superfuel. JOK has an ownership interest in CardioTabs, a company that sells omega-3 supplements.

Provenance and peer review Not commissioned; internally peer reviewed.

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