



Invited Commentary

Goldilocks and the three bonds: new evidence for the conditional benefits of dietary α -linolenic acid in treating cardiovascular risk in the metabolic syndrome

The metabolic syndrome is probably the most common purveyor of increased CVD risk in otherwise healthy, free-living populations. It consists of a constellation of CVD risk factors that are heterogeneously expressed, and have insulin resistance as a key underlying defect. While first-line treatment for this condition should include energy restriction, primarily to promote the loss of excess abdominal fat, there is still debate over the most appropriate choice of dietary fatty acids and carbohydrate to facilitate weight loss and correct metabolic dysfunction. In this issue of the *British Journal of Nutrition*, Baxheinrich *et al.*⁽¹⁾ present evidence to suggest that an energy-restricted diet, enriched with α -linolenic acid (ALA) from rapeseed oil, has greater efficacy in lowering risk factors in the metabolic syndrome than an energy-restricted diet enriched with olive oil. This study describes conditions under which dietary ALA may be of benefit to cardiovascular health, and may have found a role for this essential fatty acid in the treatment of the metabolic syndrome.

The rationale for decreasing the intake of dietary SFA in the metabolic syndrome lies not through the effects on raised serum cholesterol, which is not a defining feature of the condition, but in the potential to increase insulin sensitivity. One possible strategy for achieving this effect in practice would be to exchange dietary SFA with MUFA. In this respect, two of the largest studies to date that examined the impact of this dietary exchange in weight-maintained human subjects, with and at risk of the metabolic syndrome ('LIPGENE' (Lipids and Genes)⁽²⁾ and 'RISCK' (Reading, Imperial, Surrey, Cambridge and Kings)⁽³⁾), showed no effects of a high- and low-fat diet on insulin sensitivity. These findings highlight the limited efficacy of dietary modification for increasing insulin sensitivity in the metabolic syndrome, in the absence of weight loss. Interestingly, LIPGENE and RISCK adopted different approaches for counteracting the potentially adverse effect of increased carbohydrate in low-fat diets on serum TAG, and included either a supplement of long-chain (LC) n -3 PUFA (1.1 g/d) or foods with a low glycaemic index, respectively. Both strategies proved equally effective in limiting a carbohydrate-induced increase in serum TAG.

The metabolic effects of dietary LC n -3 PUFA (EPA + DHA), chiefly from oily fish, extend well beyond the lowering of

serum TAG, and are highly applicable to the modification of CVD risk in the metabolic syndrome. The intake of LC n -3 PUFA has been unequivocally associated with reduced CVD risk, and more specifically, reduced sudden cardiac death⁽⁴⁾. Although there is no convincing evidence that these fatty acids increase insulin sensitivity or promote weight loss, they do exert favourable effects on CVD risk factors that limit the development of atherosclerosis, and also counteract the endpoints of CHD, such as plaque rupture, thrombosis and cardiac dysrhythmia. While evidence for the anti-arrhythmic effects of LC n -3 PUFA has been elusive in recent human intervention trials⁽⁵⁾, the strong and concordant evidence for a cardioprotective role for these fatty acids makes them an essential component in dietary strategies to treat the metabolic syndrome. A more contentious issue has been whether the health benefits of dietary LC n -3 PUFA can be achieved by increasing the intake of the shorter-chain precursor of EPA and DHA, namely ALA. Estimates for the intake of dietary LC n -3 PUFA in European populations⁽⁶⁾ are several-fold below that recommended for the primary prevention of CVD (at least 0.45 g/d), a finding that reflects a mass resistance to the consumption of oily fish as the principal source of these fatty acids. When this problem is coupled to the difficulty of sustaining fish stocks, there is a clear need to find alternative dietary sources, and plant-derived ALA is an obvious choice. However, there is now a wealth of evidence to show that dietary ALA does not share the same cardioprotective relationship with CVD risk as LC n -3 PUFA, primarily because its metabolic conversion in humans to EPA and DHA is limited. The amount of dietary ALA that is converted to EPA, and especially DHA, is conditional, not on the ratio of n -6: n -3 PUFA, but on the absolute amounts of n -6 PUFA, chiefly linoleic acid (LA), and ALA⁽⁷⁾. A critical step in the conversion depends upon the activity of Δ -6 desaturase, for which dietary ALA and LA compete. Despite the enzyme expressing a preference for ALA, in most situations, LA is competitively superior to ALA on the grounds of its greater availability. Trace-labelling studies have indicated that this limits the conversion of dietary ALA to EPA and DHA *in vivo* to a maximum of about 8%, and less than 4%, respectively⁽⁸⁾, though these estimates may be significantly lower in the presence of an LA-enriched diet⁽⁹⁾.

The expectation that dietary ALA could exert effects that were equivalent to those of LC *n*-3 PUFA may have gone, but its potential to exert benefit on CVD risk has not been lost.

The study by Baxheinrich *et al.*⁽¹⁾ examined the relative impact of two energy-restricted diets for 6 months on components of the metabolic syndrome. The diets were enriched with MUFA either in the form of olive oil or rapeseed (canola) oil and closely matched in terms of their total energy contribution from carbohydrate, fat and protein. The diets were also carefully designed to be equivalent in terms of their fatty acid composition, with the exception of the rapeseed oil diet delivering four times the amount of dietary ALA (3.46 *v.* 0.78 g/d). Both diets were accompanied by significant reductions in body weight and decreases in systolic blood pressure, serum LDL-cholesterol, insulin and expression of the metabolic syndrome. In addition, the rapeseed oil diet alone was associated with significant reductions in diastolic blood pressure and serum TAG. Whether these additional findings can be ascribed to dietary ALA, or through its conversion to LC *n*-3 PUFA, raises the issue of the relative benefits of these individual fatty acids. While the most potent metabolic effects of LC *n*-3 PUFA have been more frequently ascribed to DHA, including the lowering of serum TAG and diastolic blood pressure⁽¹⁰⁾, there is evidence to support favourable effects of ALA from flaxseed oil on the latter⁽¹¹⁾. The rapeseed oil diet delivered approximately 2 and 6% of total energy from ALA and LA, respectively. This energy contribution from LA is significantly above the 1–2% of that recently shown to be optimal for the conversion of ALA (at 1–2% energy) into DHA, at least in rats⁽¹²⁾. Although the dietary conditions for the interconversion of fatty acids in animal models may not translate directly to humans, the high energy contribution from LA to the rapeseed oil diet may not have been optimal for the conversion of ALA into DHA. Unfortunately, the study did not include analysis of EPA and DHA in either serum or cell membrane phospholipids as a measure of dietary compliance and conversion of dietary ALA.

In conclusion, dietary ALA has been implicated in the beneficial effects of an energy-restricted, rapeseed oil diet on the metabolic syndrome. These effects may well depend on energy restriction and dietary conditions that include plenty of MUFA, not too much *n*-6 PUFA and just the right amount of ALA. These conditions may achieve benefits to cardiovascular health that are subtle in comparison with dietary LC *n*-3 PUFA, but are more acceptable and ecologically sustainable than oily fish.

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