Comments

Cardiovascular effects of alpha-linolenic acid – a possible role of glucagon-like peptide-1

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α-Linolenic acid (ALA; 18 : 3 n-3) is a plant-derived essential omega-3 (*n*-3) polyunsaturated fatty acid (PUFA). ALA must be obtained from the diet and is found in walnuts, rapeseed (canola) oils, flaxseeds and soya beans. ALA has been suggested to have cardiovascular benefit, albeit several, mainly observational studies have failed to demonstrate convincing results. At present, ALA supply for long-term cardioprotection is a highly controversial topic.

In a recent meta-analysis of observational studies, ALA was shown to reduce the risk of cardiovascular disease (CVD).[1] The clinical and methodological diversity among the studies included was ample and, consequently, heterogeneity was substantial. Nevertheless, the meta-analysis is comprehensive, methodologically sound and comprises 27 original studies with 251,049 individuals and 15,372 events. The work is of great value because it expands recent publications in the field by evaluating studies with dietary ALA as the exposure ($N = 13$), as well as studies using ALA biomarkers as exposure ($N = 17$). Importantly, the study is up-to-date owing to the inclusion of several recent investigations.

The overall pooled relative risk (RR) was 0.86 (95% confidence interval (CI): 0.77–0.97; $I^2 = 71.3\%$). The association was significant for dietary ALA (pooled RR: 0.90 (95% CI: 0.81–0.99; $I^2 = 49.0\%$), and near-significant in the ALA biomarker studies (pooled RR: 0.80; 95% CI: 0.63–1.03; $I^2 = 79.8\%$). For elucidation of the potential explanation for the effects of ALA on CVD, the authors suggest that ALA may exert beneficial effects on low-density lipoprotein (LDL) cholesterol, thrombosis, arrhythmias, endothelial function and inflammatory factors.

In general, there is considerable uncertainty regarding the mechanistic basis of the putative cardioprotective effects of ALA. To elucidate the potential pathways of the effects of ALA on CVD outcomes in the present as well as impending studies, we believe that one factor deserves allusion to. This factor, glucagon-like peptide-1 (GLP-1), is an incretin hormone secreted from intestinal L cells upon meal intake resulting in strong glucose-dependent insulin secretion from pancreatic β cells (the incretin effect).[2] GLP-1 furthermore decreases postprandial glucagon levels, appetite sensation, food intake and gastric emptying, and, therefore, constitutes an important regulator of normal glucose homeostasis.[2] Native GLP-1 is rapidly degraded to its inactive form, and thereby inactivated, by the ubiquitous enzyme dipeptidyl peptidase 4 (DPP-4). In the treatment of type 2 diabetes, this therapeutic limitation has been overcome by using DPP-4 inhibitors and stable GLP-1 receptor agonists with longer half-lifes.[2]

A large body of evidence suggests that GLP-1 exerts powerful cardioprotective effects.[3] For instance, preclinical and clinical studies have shown that GLP-1 and GLP-1 analogues reduce ischemic reperfusion injury and infarct size,[4,5] and, additionally, GLP-1 may exert long-term, beneficial effects on various cardiovascular parameters (such as blood pressure, heart failure, body weight, and lipid metabolism).[3,6] The promising cardiovascular findings in patients treated with GLP-1 receptor agonists are currently under investigation in four large cardiovascular outcome studies (LEADER, EXCEL, ELIXA and REWIND).[3] Likewise, the promising cardiovascular effects described for DPP-4 inhibitors are presently being evaluated in large cardiovascular outcome studies (TECOS, EXAMINE, SAVOR-TIMI and CAROLINA).

In recent years, free fatty acids (FFAs) have been positioned as potent, endogenous signaling molecules in animal and human physiology. They activate G protein-coupled receptors (GPCRs), many of which are present on the L cells where they, among many functions, facilitate stimulation of GLP-1 secretion.[7,8] Hirasawa *et al*.[9] demonstrated that the activation of one of these GPCRs, GPR120, with long-chain FFAs promoted the secretion of GLP-1. This seminal study was conducted *in vitro* and *in vivo* and included receptor isolation from a human genomic DNA fragment. Interestingly, it was further demonstrated that when stimulating STC-1 cells, from a mouse GLP-1-secreting enteroendocrine cell line, with unsaturated long-chain FFAs, a dose-dependent stimulatory effect was demonstrated, with ALA exhibiting the greatest potency. Intriguingly, in a rat study also, long-term administration (four weeks) of ALA was shown to raise GLP-1 levels via GPR120 activation, indicating that daily ALA exposure is capable of augmenting basal levels of endogenous GLP-1.[10]

Because no cogent mechanistic explanation for the improved CVD risk observed after ALA exposure has been uncovered, it might be worthy to consider the ability of ALA, as well as other omega-3 FFAs, to enhance endogenous GLP-1 secretion, putatively resulting in cardioprotection on multiple levels.[3] Indeed, this notion may also be of importance for the interpretation of similar studies (and meta-analyses),[11] though it should be recognized that several recent meta-analyses have not been able to demonstrate any cardiovascular benefit of omega-3 FFA supplementation.[12,13] Nevertheless, it is recognized that additional large, well-conducted, randomized, clinical trials are needed in order to bring clarity to this controversy. The present meta-analysis of ALA supplementation underlines this need, and thus, in striving to corroborate these most interesting findings, we suggest that GLP-1 should be included to aid in the mechanistic interpretation of the results.

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