

## **Has there been scientific evidence pointing to differences between eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)?**

There are biological differences between EPA and DHA. *In vitro*, *in vivo*, and clinical studies have reported numerous differences in the biological effects of EPA and DHA. For example, EPA has different tissue distribution, different transcriptional, antioxidant, and membrane-stabilizing effects compared to DHA or omega-3 fatty acid mixtures containing DHA.

The anti-inflammatory mechanisms of action may be different for EPA vs DHA as elucidated by data presented at the American College of Cardiology medical congress by Stephen Nicholls, MD and published in the European Medical Journal as a recap and in the Journal of the American College of Cardiology as an abstract.<sup>1,2</sup> Dr. Nicholls and colleagues studied the anti-inflammatory actions of EPA as compared to DHA in animals and cell cultures.<sup>2</sup>

- The results showed that high-dose EPA delivered to endothelial cells in culture reduced the TNF-induced acute vascular inflammation and had significantly greater effects compared with both DHA and standard fish oil dietary supplement.
- In mice, EPA, but not DHA, reduced the protein expression of markers of acute vascular inflammation in a manner that was independent of cholesterol and triglycerides.
- In another study in mice, EPA significantly reduced the gene expression of two markers of vascular inflammation (IL-1 $\beta$  and TNF- $\alpha$ ;  $p < 0.05$ ), compared with the group without treatment. Furthermore, blood EPA concentrations correlated inversely with the gene expression of these markers (IL-1 $\beta$ :  $p = 0.009$ ,  $r = -0.63$ ; TNF- $\alpha$ :  $p = 0.04$ ,  $r = -0.5$ ). DHA did not significantly reduce the gene expression of these markers.

In addition, imaging studies suggest differences between EPA and omega-3 mixtures containing DHA as seen in the HEARTS (LOVAZA®) study where the primary plaque endpoint was not met in contrast with the EVAPORATE (VASCEPA®) study where the primary plaque endpoint was met; and differences in the epicardial fat data measured by coronary CT angiography (CCTA) in the HEARTS study compared with a Japanese CCTA study with EPA studying epicardial fat via CT.<sup>3,4,5,6</sup> The evidence suggests that DHA may raise the level of “bad” LDL cholesterol, with unclear biological impacts.<sup>7,8</sup>

In cardiovascular outcomes studies, the study of pure and stable EPA has demonstrated significant clinical benefit in lowering cardiovascular risk (see discussion of the REDUCE-IT® study elsewhere on this website) while cardiovascular outcomes studies of products which contain DHA have repeatedly failed to demonstrate cardiovascular benefit (see discussion of VITAL, ASCEND, STRENGTH and meta-analysis discussed elsewhere on this website).

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<sup>1</sup> Pisaniello AD, Nicholls SJ, Ballantyne CM, Bhatt DL, Wong ND. Eicosapentaenoic acid: atheroprotective properties and the reduction of atherosclerotic cardiovascular disease events. *EMJ*. 2020;5:29-36.

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- <sup>2</sup> Di Bartolo BA, Liu G, King PM, Gibson RA, Tan JTM, Nicholls SJ. Eicosapentaenoic acid ameliorates vascular inflammation: a mechanistic rationale for its atheroprotective effects [abstract]. *J Am Coll Cardiol* 2020;75(11 suppl 1):3661.
- <sup>3</sup> Alfaddagh A, Elajami TK, Ashfaque H, Saleh M, Bistrrian BR, Welty FK. Effect of Eicosapentaenoic and Docosahexaenoic Acids Added to Statin Therapy on Coronary Artery Plaque in Patients With Coronary Artery Disease: A Randomized Clinical Trial. *J Am Heart Assoc*. 2017;6(12):e006981.
- <sup>4</sup> Budoff MJ, Bhatt DL, Kinninger A, Lakshmanan S, Muhlestein JB, Le VT, May HT, Shaikh K, Shekar C, Roy SK, Tayek J, Nelson JR. Effect of icosapent ethyl on progression of coronary atherosclerosis in patients with elevated triglycerides on statin therapy: final results of the EVAPORATE trial. *Eur Heart J*. 2020;41(40):3925-3932.
- <sup>5</sup> Asbeutah AA, Amangurbanova M, Waseem S, Mirza H, Welty FK. Effect of Eicosapentaenoic Acid and Docosahexaenoic Acid on Epicardial Fat Volume; Results From a Randomized Controlled Trial [abstract]. *Circulation*. 2020;142:A13314.
- <sup>6</sup> Sato T, Kameyama T, Ohori T, Matsuki A, Inoue H. Effects of eicosapentaenoic acid treatment on epicardial and abdominal visceral adipose tissue volumes in patients with coronary artery disease. *J Atheroscler Thromb*. 2014;21(10):1031-43.
- <sup>7</sup> Wei MY, Jacobson TA. Effects of eicosapentaenoic acid versus docosahexaenoic acid on serum lipids: a systematic review and meta-analysis. *Curr Atheroscler Rep*. 2011;13(6):474-83.
- <sup>8</sup> Jacobson TA, Glickstein SB, Rowe JD, Soni PN. Effects of eicosapentaenoic acid and docosahexaenoic acid on low-density lipoprotein cholesterol and other lipids: a review. *J Clin Lipidol*. 2012;6(1):5-18.