

## COMMENTS AND RESPONSES

### Response to Comment on: Satoh-Asahara et al. Highly Purified Eicosapentaenoic Acid Increases Interleukin-10 Levels of Peripheral Blood Monocytes in Obese Patients With Dyslipidemia. *Diabetes Care* 2012; 35:2631–2639

**W**e appreciate the comments made by Professor Nonogaki regarding our article entitled “Highly Purified Eicosapentaenoic Acid Increases Interleukin-10 Levels of Peripheral Blood Monocytes in Obese Patients With Dyslipidemia,” and we sincerely respond to his comments here (1).

First, Professor Nonogaki described a recent systemic review and meta-analysis demonstrating that supplementation with omega-3 polyunsaturated fatty acids is not associated with a lower risk of all-cause mortality or major coronary events (MCE). However, the median dose of omega-3 including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in 20 trials referenced by this meta-analysis was 1.0 g/day, and the median dose of EPA in these 20 trials was only 0.46 g/day. However, in our study, 1.8 g/day of highly purified EPA was administered (2). In the Japan EPA Lipid Intervention Study (JELIS), 1.8 g/day of highly purified EPA exhibited beneficial effects of reducing MCE by 19%, in addition to statins. Therefore, the EPA dose used in our study is completely different from that in studies (other than JELIS) referenced in the meta-analysis.

Professor Nonogaki also described a population-based cross-sectional study (ERA JUMP Study) reporting that DHA, but not EPA, has an inverse association with the carotid intima-media thickness.

However, the OCEAN Study showed that the carotid atherosclerotic plaques in patients treated with omega-3 polyunsaturated fatty acid ethylesters (EPA and DHA) readily incorporate EPA rather than DHA, and that the EPA content of plaque phospholipids was inversely associated with plaque instability and inflammation (3). In addition, another study demonstrated that in type 2 diabetic patients who are not treated with statins, 1.8 g/day of highly purified EPA significantly reduced carotid intima-media thickness and the pulse wave velocity, and that the administration of EPA was a significant and independent factor associated with an annual improvement of the mean carotid intima-media thickness (4). Accordingly, it is important that the serum EPA or EPA-to-arachidonic acid (AA) ratio can be associated with carotid atherosclerosis in dyslipidemic patients without a history of coronary events and who are not treated with statins.

In the subanalysis of the secondary prevention of coronary artery disease in JELIS, the incidence of cardiac death or myocardial infarction was significantly lower in patients with the highest EPA-to-AA ratio than in those with the lowest ratio. In addition, in all JELIS participants, the highest level of EPA, but not DHA, was inversely associated with the risk of MCE. Other studies also suggested that a decreased serum EPA-to-AA ratio is significantly associated with the coronary plaque score and major adverse cardiac events in patients with MCE. Recently, the Hisayama Study suggested that a lower EPA/AA level is associated with a greater risk of death from cardiovascular causes in the general Japanese population (5). Taken together, these findings suggest that the decreased serum EPA-to-AA ratio is associated with atherosclerosis and cardiovascular events in both subjects with and without a history of coronary diseases. Further long-term prospective cohort and intervention studies are needed to elucidate the differentiation and influence of EPA and DHA on atherosclerosis and cardiovascular events in patients with lifestyle-related diseases without coronary events.

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