Is there a new component of the Mediterranean diet that reduces inflammation?\textsuperscript{1,2}

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In this issue of the Journal, Detopoulou et al (1) report that higher dietary intakes of choline and betaine in the Greek population reduce inflammation as assessed by several biomarkers in blood. The effects of dietary choline and betaine on inflammatory biomarkers were of the same magnitude as those reported for the Mediterranean diet. More than 3000 persons were studied in the cross-sectional ATTICA study, and individuals in the highest tertile for dietary intake of choline and betaine had significantly lower plasma C-reactive protein, interleukin-6, and tumor necrosis factor-\(\alpha\) concentrations than did persons in the lowest tertile of intake. This new observation supports the findings of several other major population studies during the past 2 y on the associations between high dietary intakes of choline and betaine and markers of disease: plasma total homocysteine [a risk factor for heart disease; inverse association in the Framingham Study (2) and in the Nurses’ Health Study (3)], atherosclerosis [marginally positive association in the Atherosclerosis Risk In Communities Study (4) and in the European Prospective Investigation into Cancer and Nutrition (5)], and colorectal adenoma (positive association in the Nurses’ Health Study; 6). An article on these nutrients and their associations with breast cancer in a large population study is under review (negative association in the Long Island Breast Cancer Study). Why is there such interest in dietary choline and betaine?

Choline is derived not only from the diet but also through biosynthesis in the liver (7). Choline is used to make membrane phospholipids and to make acetylcholine, a neurotransmitter (7). Betaine, a metabolite of choline, is an important methyl group donor used in the remethylation of homocysteine to form methionine (6). When deprived of dietary choline and betaine, most adult men and postmenopausal women develop a deficiency syndrome characterized by signs of organ dysfunction (fatty liver as well as liver or muscle cell death) (8). Only a subset of premenopausal women developed such a deficiency. The difference in requirement occurs because estrogen induces the liver PEMT gene, which allows premenopausal women to make more of their needed choline endogenously (9). In addition, there is significant variation in the dietary requirement for choline that can be explained by common genetic polymorphisms (10). Choline is critical during fetal development (rodents), when it influences stem cell proliferation and apoptosis, thereby altering brain structure and function (7). Similarly it influences neural tube development in humans (7). When food-composition tables that include these nutrients recently became available from the US Department of Agriculture (Internet: www.nal.usda.gov/fnic/foodcomp/Data/Choline/Choline.html), it became possible to examine the associations between dietary intake and chronic diseases.

Is the association between choline and betaine intake and inflammation likely to be real? Diets high in choline are also high in eggs and meat; diets high in betaine are likely to be high in plant foods. In US populations the average choline intake was 320–380 mg/d with a 3-fold variation between highest and lowest intakes (2, 4, 6). In the Greek population, choline intake and variation was similar. In US populations, the average betaine intake was shown to be 110–190 mg/d (2, 4, 6); however, in Greeks, the average intake was shown to be substantially higher (310 mg/d). Betaine is usually a component of plants, which suggests that Greeks have a different dietary pattern than do Americans; ie, Greeks consume more of a plant-based diet than do Americans. Because Detopoulou et al reported similar effects on inflammation for both choline and betaine intakes, it is reasonable to conclude that the antiinflammatory effect they report was not exclusively due to a difference in meat, egg, or vegetable intake. Epidemiologic studies have limitations and can only suggest associations; they can easily be confounded. For example, in the Nurses’ Health Study (6), women who ate more choline in their diets also exercised more, ate more folic acid, smoked less, and used aspirin more. A higher betaine intake was associated with a lower body mass index (6). However, there are plausible biological mechanisms that could underlie the observations of decreased inflammation in Greeks who consumed more betaine and choline. The finding that both choline and betaine had an effect suggests that the response was mediated by some common pathway, possibly methylation and the removal of homocysteine. Diets high in choline and betaine lower plasma homocysteine concentrations (2, 3), as do treatments with dietary supplements of these nutrients (11, 12). Also, patients with homocysteinuria have elevated biomarkers of inflammation (13). It is possible that epigenetic mechanisms, via the methylation of promoter regions of genes involved in inflammation, are responsible for the observed association between dietary choline

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and betaine and inflammation (7). Choline-deficient humans overexpress genes in the immune-inflammatory response and lymphocyte differentiation-activation gene ontology groupings (14). Exposure to oxidative stress is a potent trigger for inflammation. Betaine is formed from choline within the mitochondria, and this oxidation contributes to mitochondrial redox status. Choline deficiency is associated with leaky mitochondria, leakage of free radicals, and damage to DNA (15–17). Thus, there are multiple potential mechanisms whereby diets lower in choline and betaine might result in increases in biomarkers of inflammation in healthy humans. If the association between choline and betaine and inflammation can be confirmed in studies of other populations, an interesting new dietary approach may be available for reducing chronic diseases associated with inflammation.

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