Atherosclerosis: an environmental disease impacted by genetics

The enzyme 5-lipoxygenase catalyzes the conversion of arachidonic acid to leukotrienes, which are involved in the inflammatory process. Chronic inflammation is believed to play an important role in the development of atherosclerosis. In the present study, 5-lipoxygenase genotypes, carotid-artery intima-media thickness (a measure of the severity of atherosclerosis), and markers of inflammation were determined in 470 healthy men and women (aged 40-60 years) participating in the Los Angeles Atherosclerosis Study. Variant 5-lipoxygenase genotypes (lacking the common allele) were found in 6% of the participants, whereas 94% had at least one copy of the common allele. The mean carotid-artery intima-media thickness was 12% greater (p < 0.001) among carriers of two variant alleles than among carriers of the common allele. The increase in intima-media thickness associated with the genetic variant was similar in this cohort to that associated with diabetes. Increased dietary intake of arachidonic acid significantly increased the atherogenic effect of the variant genotype, whereas increased intake of marine omega-3 fatty acids blunted the effect. In contrast, neither of these dietary factors was associated with intima-media thickness in subjects carrying the common allele.

The plasma level of C-reactive protein (a marker of inflammation) was two-fold higher (2.6 vs. 1.3 mg/L; p = 0.007) among carriers of two variant alleles than among carriers of the common allele.

Comment: Atherosclerosis is considered a polygenic disease, in that numerous different genetic influences are involved in its development. Some genetic variations interact with specific environmental factors. For example, people who carry a gene for iron overload might be able to reduce their risk of atherosclerosis by avoiding excessive intake of iron. Those with the common genetic variant of the methylenetetrahydrofolate reductase enzyme have a higher-than-normal requirement for folic acid, and may be able to reduce their risk of atherosclerosis by increasing their intake of folic acid. Some people who develop premature atherosclerosis have elevated homocysteine levels due to a defect in the vitamin B6-dependent enzyme cystathionine synthase; in those people homocysteine levels can be reduced by supplementing with vitamin B6.

The results of the present study indicate that about 1 in 16 people have a genetic variant of an enzyme that influences fatty acid metabolism. People with this variant are more susceptible to the potential adverse effects of eating meat (which is high in arachidonic acid), and more likely to be protected by eating fish, than are people with the more common variant. Genetic factors may explain why some people can abuse their bodies and not develop chronic illness, while others seem to suffer the consequences of even minimal dietary and lifestyle indiscretions.


Does vitamin E cause heart failure?

In the Heart Outcomes Prevention Evaluation (HOPE) study, 9,541 patients with cardiovascular disease or diabetes, plus one other cardiovascular risk factor, were randomly assigned to receive, in double-blind fashion, 400 IU/day of vitamin E (RRR-alpha-tocopheryl acetate) or placebo, and either an angiotensin-converting-enzyme inhibitor (ramipril) or placebo, for a mean of 4.5 years. Results of the study showed that ramipril was beneficial, but vitamin E was not.

At the end of the study, 6,786 patients agreed to enter a continuation phase, in which all patients received ramipril, and 3,994 patients were randomly assigned to receive 400 IU/day of vitamin E or placebo for an additional 2.6 years, producing a total study duration of 7.1 years. At the end of the first part of the study, the incidences of heart failure events and hospitalizations for heart failure were higher in the vitamin E group than in the placebo group, but the differences were of only borderline statistical significance. The results from the continuation phase, when combined with the original results, did achieve statistical significance: heart failure events occurred in 14.7% of those using vitamin, compared with 12.6% of those using placebo (16.7% increase) and hospitalizations for heart failure occurred in 5.8% and 4.2% of patients, respectively (38.1% increase).

Comment: Vitamin E has a long and controversial history as a potential treatment for heart disease. While some large-scale clinical trials have found vitamin E to be beneficial, the majority of studies have found little or no effect of vitamin E. The HOPE trial is the first to suggest that vitamin E actually increases the risk of certain types of heart disease.

All of the studies of vitamin E supplementation for heart-disease prevention have used alpha-tocopherol, whereas the vitamin E in food contains four different isomers: alpha-, beta-, gamma-, and delta-tocopherol. An increasing body of evidence indicates that gamma-tocopherol has a strong cardioprotective effect. Moreover, supplementing with large doses of alpha-tocopherol results in a decline in serum concentrations of gamma-tocopherol. It is possible, therefore, that the positive effects of alpha-tocopherol are negated by a reduction in gamma-tocopherol levels. That possibility is supported by epidemiological studies indicating that vitamin E from food protects against heart disease, whereas vitamin E from supplements (e.g., alpha-tocopherol alone) does not. Future vitamin E studies should use "mixed tocopherols" that contain the four vitamin E isomers in proportions that are similar to those found in the diet.


Vitamin D deficiency related to diabetes and insulin resistance

Two recent studies have shown that vitamin D deficiency may be a contributing factor in some cases of diabetes and/or metabolic syndrome (insulin resistance). In a study of 126 healthy volunteers (mean age 26 years) with normal glucose tolerance, there was a significant positive correlation (p < 0.0001) between the serum 25-hydroxyvitamin D concentration (a measure of vitamin D nutritional status) insulin sensitivity,