Diet/Genetic Interactions and Their Effects on Inflammatory Markers
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The importance of a healthy diet to living well is well recognized. A growing array of experimental, epidemiological, and clinical studies have revealed an association between pro-inflammatory responses and the progression of numerous serious disease states, including the metabolic syndrome, type 2 diabetes, and cardiovascular diseases. Further studies have established a “diet/genetic interaction” that further modulates markers of inflammation, producing both positive and negative effects, depending on the net changes in gene expression. Yet, there are few studies that reveal the mechanisms underlying this modulation of the inflammatory response. Highlighted here are several recent and ongoing studies that investigate the mechanisms underlying the effects of diet/genetic interactions on inflammatory biomarkers, followed by a discussion of to what extent these interactions may translate into healthier aging and increased longevity. Whether these interactions translate into healthier aging and increased longevity remains to be determined; however, the prospects are enticing.

Key words: atherosclerosis, adiponectin, cardiovascular disease, cardiovascular risk, C-reactive protein, genetic interaction, inflammation, intercellular cell adhesion molecule-1, interleukin-6, Mediterranean diet, monounsaturated fatty acid, polymorphism, polyunsaturated fatty acid, resolving E1, vascular cell adhesion molecule-1

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INTRODUCTION

The association between diet, particularly dietary fat intake, and cardiovascular risk has been demonstrated in a number of epidemiological and interventional trials. However, the results of these trials also indicate that all fats are not equal; while some fats increase cardiovascular risk, others might be cardioprotective. Further, the current evidence supports that genetic factors play a significant role in interindividual differences accounting for disease predisposition as well as response to dietary recommendations. Thus, a diet that confers protection against cardiovascular disease (CVD) in one individual may have no effect, or even a negative effect in another. As the cellular mechanisms responsible for the progression of atherosclerosis, the underlying pathology of CVD, becomes better understood, it becomes increasingly clear that inflammation is a major component of the risk for CVD. Inflammation is a key component of atherogenesis, contributing to the initiation of an atherosclerotic lesion, its growth and development, and rupture of the unstable plaque to initiate a clinical cardiovascular event. The inflammatory response can be both amplified and ameliorated by changes in dietary fat intake, through modulation of both pro- and anti-inflammatory mechanisms (Figure 1). Finally, the interaction between diet and genetic variation can create a wide spectrum of outcomes in different individuals.

IMPACT OF THE DIET ON CARDIOVASCULAR RISK

One diet promoted for its cardiovascular benefits is the “Mediterranean diet” (MD), which is based upon a high consumption of fruits and vegetables, bread, wheat and other grains, olive oil, and fish, making it low in saturated fat, high in monounsaturated fat, and high in dietary fiber. However, although epidemiological and interventional studies have reported a lower incidence of CVD among people eating the MD, few interventional studies have quantified and explained its health benefits.
benefits. In this regard, the Lyon Heart Study reported a 50–70% reduction in cardiovascular risk in patients with established CVD who consumed a modified MD, compared with patients who received no dietary advice. However, these dramatic effects need to be replicated by additional intervention trials.

This is the purpose of the PREDIMED Study, a primary prevention interventional study designed to further assess the cardiovascular benefits of the MD. The specific aim of this multicenter study based in Spain is to quantify the effects of the MD on CVD risk over a three-year period, including cardiovascular death, non-fatal myocardial infarction and non-fatal stroke. The trial will also establish the impact of the MD on a range of cardiovascular risk factors including changes in blood pressure, body weight, adiposity measures, blood sugar, lipid profile, and a number of markers of inflammation. Enrolling 9,000 individuals at high risk of CVD, participants are randomly assigned to one of three “beneficial” diets: a low fat diet; an MD featuring consumption of 1 liter per week of extra virgin olive oil (MD plus olive oil); or an MD plus 30 grams per day of tree nuts.

While the results of this trial will not be available until 2010, a pilot trial has provided valuable insight into the effect of these dietary interventions on inflammatory biomarkers, and other markers of cardiovascular risk. This trial enrolled 772 asymptomatic individuals with a high CVD risk: their mean age was 69 years and the mean body mass index (BMI) bordered on obese, the majority were diagnosed with type 2 diabetes, hypertension, and abnormal lipid levels, and most had a family history of CVD. After three months of dietary intervention identical to that outlined above, changes in cardiovascular risk factors and inflammatory biomarkers were assessed, with promising results.

The low-fat diet produced a reduction in BMI but had no significant effect on adiposity, blood pressure or cardiovascular risk factors, indicating the limited value of this intervention over the trial period. The MD plus olive oil and MD plus nuts diets, however, produced significant decreases, compared to the low-fat diet, in systolic and diastolic blood pressure, fasting glucose concentration, and insulin resistance; significant increases in high-density lipoprotein cholesterol (HDL-C) concentrations were also observed in both groups. In addition, significant decreases in total cholesterol and triglyceride concentrations were noted in the MD with nuts diet, as compared to the low-fat diet group.

Beneficial changes were similarly observed for numerous inflammatory biomarkers in the MD plus olive oil and MD plus nuts groups (Figure 2). Both interventions resulted in significant reductions in plasma concentrations of the pro-inflammatory biomarkers interleukin-6 (IL-6), intercellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1). Also, the MD plus olive oil was associated with a significant reduction in plasma concentrations of the

Figure 1. Interaction of diet and genetic factors can affect both inflammatory biomarkers and clinical conditions.

Figure 2. Mean changes from baseline in plasma concentrations of the inflammatory biomarkers C-reactive protein (CRP), interleukin-6 (IL-6), and intravascular cell adhesion molecule-1 (ICAM-1) following three months consuming a Mediterranean-style diet with extra virgin olive oil (MD), MD augmented with nuts (MD+N), or a low fat diet (LF). *P<0.003 and **P<0.018 for difference from baseline. Reprinted from Estruch et al. (Ann Intern Med. 2006;145:1–11) with permission from the American College of Physicians.
acutely, the only significant effect observed in the low-fat diet group was an increase in VCAM-1 and ICAM-1 levels.

Another trial supporting the anti-inflammatory effects of the MD was a rather small study in which 16 healthy men consumed the following three diets in a randomized crossover design: 1) the MD; 2) a low-fat/high-carbohydrate diet supplemented with n-3 polyunsaturated fatty acids (PUFAs); and 3) a Western diet high in saturated fats. At the end of each dietary period, the levels of activation of the pro-inflammatory transcription factor nuclear factor-kappa B (NF-κB) in monocytes, and plasma concentrations of VCAM-1, were determined. Compared with the Western diet, the MD was associated with a significant decrease in the levels of activation of NF-κB and plasma VCAM-1 concentration, while the low-fat diet was associated with a significant decrease in plasma VCAM-1 concentration only.

Taken together, these data provide an enticing preview of what PREDIMED could demonstrate. Diets rich in extra-virgin olive oil appear to improve lipid profiles, reduce blood pressure and insulin resistance, and promote a less inflammatory environment by reducing the expression and/or activation of pro-inflammatory biomarkers, and thus may be associated with cardiovascular protection.

GENETIC INTERACTION AFFECTS THE RESPONSE TO DIETARY MODIFICATION

Genetic make-up can also influence the effect of dietary modification on cardiovascular risk factors, as can be seen with the interaction between a polymorphism of the adiponectin gene and low-fat diet on insulin resistance.

Adiponectin is a compound exclusively secreted by adipose tissue that modulates a number of processes, including glucose regulation and fatty acid catabolism. It is considered a promoter of anti-inflammatory conditions, due to its inhibition of tumor necrosis factor alpha (TNFα)-induced NF-κB activation, inhibition of expression of adhesion molecules, and reduction of foam cell formation. Whereas low adiponectin levels are associated with obesity, type 2 diabetes, CVD, and insulin resistance, high adiponectin levels are associated with a healthy diet, lean body mass, and a lack of the aforementioned disease states.

The adiponectin gene includes a number of single nucleotide polymorphisms, including the ADIPOQ 276(G/T) polymorphism. The variant allele has been associated with insulin resistance and lower adiponectin levels in a Japanese population, with the metabolic syndrome in Italians in a haplotype with another polymorphism, 45(T/G), and with conversion from impaired glucose tolerance to diabetes in the predominantly Caucasian population enrolled in the STOP-NIDDM study. In Koreans, carriers of the G allele had lower plasma adiponectin concentrations and higher markers for oxidative stress than TT homozygotes with a similar BMI. These results suggest that in this population, the presence of the 276G allele could be associated with increased cardiovascular risk.

Currently, another diet/genetic interaction study is examining the mechanisms underlying the interaction of genetics, lipid-lowering drugs, and diet, known as the GOLDN study. While the results remain forthcoming, the aim of this study is to characterize the genetic basis of the variable response of triglycerides (TGs) to two interventions, one that raises TGs acutely (increased dietary fat load), and one that lowers TGs (fenofibrate treatment). A total of 1,200 subjects with ages ranging from 18 to 92 years are currently recruited from two genetically homogeneous centers (Minneapolis and Salt Lake City) with predominantly Caucasian populations. Ultimately, the results of this study should shed light on how diet/genetic interactions influence susceptibility to developing the metabolic syndrome.

DIET CAN AFFECT CARDIOVASCULAR RISK ASSOCIATED WITH GENETIC VARIATION

Another example of the significance of diet/genetic interaction can be seen in the relationship between polymorphisms of the arachidonate 5-lipoxygenase (5-LO) promoter, dietary fat intake, and carotid intima-media thickness (CIMT; a surrogate marker for atherosclerosis). Carotid intima-media thickness was significantly higher in individuals homozygous for the variant promoter region alleles compared with those who possessed at least one copy of the common allele, signifying that the variant alleles increased cardiovascular risk. This relationship between genotype and cardiovascular risk was not affected by dietary saturated fat, or monounsaturated fat intake. However, increased intake of arachidonic acid and other n-6 PUFAs increased the atherosclerotic risk associated with the variant alleles. Conversely, the increase in CIMT associated with the variant alleles was eliminated by a high intake of n-3 PUFAs.

Of all the fatty acids, the n-3 PUFAs possess the most potent inflammatory suppression activities. Recent studies have identified these effects to be due, in part, to the generation of a potent anti-inflammatory derivative of n-3 PUFAs, resolvin E1 (RvE1). Resolvin E1 is synthesized through the actions of either cyclooxygenase-2 (COX-2), which is stimulated by aspirin, or cytochrome P450 monooxygenase, which converts eico-
sapentaneic acid (EPA) to 18-hydroxyeicosapentaneoic acid, which is further converted to RvE1 by a leukocyte 5-LO-like reaction.32

Resolvin E1 manifests its anti-inflammatory effects, in part, by decreasing NF-κB activation. This is an important cascade, as it may explain the results of studies of dietary n-3 PUFA intake and EPA level that conflictingly show either significant or non-significant protective effect on various inflammatory and CVD biomarkers.7 That is, it may be that a specific genotype and/or levels of these proteins/compounds (EPA, COX-2, P450, NF-κB, etc.) must be present in the appropriate combination within this molecular pathway, in order to witness a significant anti-inflammatory endpoint. Using these targets, additional investigations are required to explain the observed variability.

Finally, it must be remembered that diet might have other complex and indirect effects on the inflammatory milieu and overall health. For example, very high dietary fat intake leads to increased cholecystokinin levels, a peptide hormone of the gastrointestinal system responsible for stimulating the digestion of fat and protein, which ultimately triggers the cholinergic anti-inflammatory pathway by means of the vagus nerve.33 Also, resveratrol, a component of red wine under study due to its antioxidant and potential cancer-fighting properties, has recently been shown to have a protective effect on the liver health and survival of mice fed a high-calorie diet.34 Its potential anti-inflammatory effects need further study, especially considering it has recently been identified as an inhibitor of NF-κB expression.35

CONCLUSIONS

In summary, it is clear that a “good” diet can promote health through its effect on the inflammatory response. This can be mediated through reduced expression of pro-inflammatory mediators like TNF-α, VCAM-1 or ICAM-1, as well as by enhancing anti-inflammatory moieties such as adiponectin or RvE1. The net effect of diet is, however, also dependent on genetics; polymorphisms in genes such as those encoding adiponectin or 5-LOX can significantly modify the effect of diet on inflammation, and thereby its effect on CVD, type 2 diabetes and other diseases of aging (Figure 2).

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