Review

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Nutrigenetics, Plasma Lipids, and Cardiovascular Risk

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Editor's note: The Figure in this article is available online as a PowerPoint slide at www.adajournal.org.

ABSTRACT

Cardiovascular disease (CVD) results from complex interactions between genetic and environmental factors. The evidence supports that gene–environment interactions modulate plasma lipid concentrations and potentially CVD risk. Several genes (eg, apolipoprotein A-I and A-IV, apolipoprotein E, and hepatic lipase) are providing proof-of-concept for the application of genetics in the context of personalized nutrition for CVD prevention. The spectrum of candidate genes has been expanding to incorporate those involved in intracellular lipid metabolism and especially those transcription factors (ie, peroxisome proliferator activator receptors) that act as sensors of nutrients in the cell (eg, polyunsaturated fatty acids) to trigger metabolic responses through activation of specific sets of genes. However, current knowledge is still very limited and so is the potential benefit of its application to clinical practice. Thinking needs to evolve from simple scenarios (eg, one single dietary component, a single nucleotide polymorphism and risk factor) to more realistic situations involving multiple interactions. One of the first situations where personalized nutrition is likely to be beneficial is in patients with dyslipidemia who require special intervention with dietary treatment. This process could be more efficient if the recommendations were carried out based on genetic and molecular knowledge. Moreover, adherence to dietary advice may increase when it is supported with information based on nutritional genomics, and a patient believes the advice is personalized. However, a number of important changes in the provision of health care are needed to achieve the potential benefits associated with this concept, including a teamwork approach with greater integration among physicians, food and nutrition professionals, and genetic counselors.
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The first century of atherosclerosis research has been dominated by the lipid hypothesis. Even when new hypotheses were brought to the table (eg, oxidation hypothesis), efforts were made to fit them into the lipid context (eg, oxidized low-density lipoprotein [LDL]). It is difficult to pinpoint when and where the initial connection between lipids and disease was made, but one of the most influential works on record goes back to the beginning of the 20th century when Nikolaj N. Anitschkow established the cholesterol-fed rabbit as a model for atherosclerosis research (1). Even earlier, during the 19th century, some clues were already apparent through uncommon case reports of children with xanthomas that were, in most cases, considered a dermatological problem. However, some of these children went on to develop severe and premature heart problems resulting from what we know today to be familial hypercholesterolemia due to mutations in the LDL receptor gene.

One wonders how different the field of atherosclerosis research might have been had Anitschkow decided to use an animal much more resistant to diet-induced atherosclerosis, such as rats or mice. During the ensuing decades, atherosclerosis moved from sporadic case reports to become a major public health concern and the diet–heart hypothesis was developed. It proposes a sequence of etiological relationships between the saturated fat content of a diet, a person's serum cholesterol level, and the development of atherosclerosis. From the very beginning, this diet–atherosclerosis connection was far from being unanimously embraced by the sci-

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entific community. A notable early example of this enduring controversy was Keys vs Pickering (2). The venue was the World Health Organization, Geneva, Switzerland, circa 1955. Ancel Keys put forward his ideas about diet and heart disease expecting to be accepted on the spot, but he was challenged by Sir George Pickering, who, according to witnesses, said: "Yes, and Professor Keys would you be kind enough to cite for us the principal piece of evidence that you think supports this diet–heart theory of yours?" Keys' evidence at that time was not convincing and his hypothesis was not accepted, driving him to build the evidence that would allow him to prove his point. This encounter was one of the driving forces behind the Seven Countries Study, a landmark in early nutritional epidemiology (3). This study, despite its shortcomings, solidified for many the notion that dietary factors and, more specifically dietary fat and cholesterol, were responsible in great part for the rise in cardiovascular disease (CVD) experienced in Western and industrialized societies during the 20th century. Almost 100 years after Anitschkow's experiments and about 50 years since the launching of the Seven Countries Study, and with thousands of dietary experiments of varied nature reported in the scientific literature, the polemic continues about the role of diet in the development of CVD (4-6). Whereas medical societies and government agencies have embraced the concept of nutrition as a major player in the epidemic of CVD and potentially in its control (6), some scientists remain skeptical about the diet–cholesterol–heart disease connection (4,5). They argue that knowledge and dietary recommendations relating to cholesterol, dietary fat, and coronary heart disease are the outcome of complex social negotiations that can only be understood in their cultural, commercial, and political contexts (7). Even those who have embraced the diet–heart hypothesis maintain their own differences of opinion by disagreeing about what constitutes the optimal diet for atherosclerosis prevention and therapy (8).

The reason for this long-lasting controversy probably lies with the oversimplification of both the problem(s) and the solution(s). The driving force of the atherosclerotic process cannot be restricted exclusively to lipid disorders but rather to a constellation of risk factors. Likewise, dietary factors are just part of a collection of behavioral and environmental factors that may disrupt metabolic balance and predispose a person to the disease. With this in mind it is not surprising that traditional one-size-fits-all recommendations are not yielding the anticipated benefits nor have they reached consensus within the scientific community.

From the world of mathematics we know that for any given system of equations there are exactly three possibilities for the solution: 1) there will not be a solution, 2) there will be exactly one solution, or 3) there will be multiple possible solutions. Experience, as described earlier, supports the notion that solutions exist and that continuing to search for one single solution may not work. Therefore, the possibility that there are multiple solutions is the most likely in our context. Considering the myriad environmental risk factors that interact with the genetic component of CVD and the fact that several million genetic polymorphisms are present in the human genome making each one of us unique, the multiple solutions option seems the most plausible. The challenge is to find out which one is the best for each individual (9). Providing an (almost) infinite number of solutions is not possible and even considering a large number of solutions will not be practical. Action in the right direction has been initiated with the introduction of the new US Department of Agriculture MyPyramid (10), which embraces the motto "one size does not fit all." However, this effort toward personalization barely scratches the surface of the potential for individualization of therapeutic recommendations that can result from nutritional genomics.

In the field of nutritional genetics (nutrigenetics), researchers are studying gene–diet interactions in an effort to better understand factors mediating individual response to dietary interventions. The scientific literature is replete with accounts of interindividual variability in response to specific dietary factors (such as high or low intake of total fat or saturated fat). Exploration of the interactions between genetic variations and diet are providing the proof of concept to support the notion that more individualized nutrition recommendations are required to address the interplay of dietary factors and genetic variations on CVD risk. Given the current evidence and interest in nutrigenetics and the current technologies available, it is possible that the much-needed knowledge will accumulate at a faster pace in the coming years, getting to a point at which findings can be translated into practical applications. However, this will require translators and a parallel effort is needed to educate a new generation of health professionals (eg, physicians and dietitians) who will be fluent in both nutrition and genetics. The American Dietetic Association has voiced repeatedly this need and opportunity for a decade (11-13) and more vehemently in recent months (14-16).

This review describes some of the advances in nutritional genomics in relation to CVD and the lipid hypothesis. This work is not intended by any means to be comprehensive, as several such reviews have recently been published (17-19). Rather, the focus will be on presenting a window of evidence as well as the challenges ahead.

CANDIDATE GENES INVOLVED IN THE METABOLISM OF CIRCULATING LIPIDS

CVD, like most common diseases, results from interactions between genetic factors and the environment (nongenetic factors). Once the genetic basis of a disease has been established, the next step is to identify the main contributing genes (20-22), as well as the genetic variants that may modulate disease risk. In this regard, genetic variants for many lipid-related genes have been studied for the past 2 decades, resulting in a plethora of reports associating genetic factors with abnormal lipid metabolism and plasma lipoprotein profiles and even with disease risk. Unfortunately, many of the initial claims have not been replicated and only a few genes have shown some consistency in their associations. Some of these genes are: apolipoprotein E in terms of associations with total cholesterol and LDL cholesterol (23); cholesteryl ester transfer protein with high-density lipoprotein

(HDL) cholesterol (24), and lipoprotein lipase and apolipoprotein A-V with triacylglycerol (25,26) concentrations.

REGULATION OF CIRCULATING LIPOPROTEINS: GENES VS ENVIRONMENT

Gene–environment interaction refers to the differential phenotypic effects of different environments on individuals with the same genotype, or to the differential effects of the same environment on individuals with different genotypes (27). Genetic variation and the different individuals' responses to environmental factors present an opportunity and a challenge to CVD prevention. Therefore, the debate over nature vs nurture needs to be put aside in favor of efforts to exploit every opportunity to study both environmental and genetic factors to improve both CVD prevention and treatment.

In studying the interaction between genes and the environment, some researchers prefer to use the concept of context-dependent genetic effect, which involves gene–gene interactions (epistasis) as well as the pure gene–environment interactions (28). The most active area relates to gene–diet interactions, a notion that has been proposed for several decades to explain some of the observed interindividual dietary responses to specific nutritional recommendations and dietary interventions (29). However, it has not been until recent years that researchers, supported by adequate technology, have begun to explore its molecular basis.

GENE–DIET INTERACTIONS

Interindividual Variability

It is well known that the effect of dietary changes on plasma lipid concentrations differs significantly between individuals (30-32). Some individuals appear to be relatively insensitive (hyporesponders) to dietary intervention, whereas others (hyperresponders) have enhanced sensitivity (31). Therefore, low-fat diets can result in reduced plasma HDL and/or increased triacylglycerol concentrations (32) that may be particularly harmful for some people. For example, it has been shown that individuals with a predominance of small, dense LDL particles (subclass pattern B), a phenotype that is associated with an increased risk of coronary heart disease, benefit more from a low-fat diet (33) than do those with the subclass pattern A (larger LDL particles). Indeed, the latter group exhibited a more atherogenic pattern B subclass after consuming a low-fat diet. Therefore, increasing numbers of intervention studies are focusing on the interindividual differences in response to diet rather than on the mean effect. Moreover, there is increasing evidence supporting that this variability in response is an intrinsic characteristic of an individual, rather than being the result of different dietary compliance with the experimental protocols. Jacobs and colleagues (34) found that individual triacylglycerol responses to a high-fat or to a low-fat diet were vastly different, suggesting that many patients with hypertriglyceridemia are not treated optimally if general advice for either a low-fat or a high-fat diet is given. Therefore, studying the reasons for this variation will allow us to better identify individuals who can benefit from a particular dietary intervention. Obviously, this is not an easy task and some authors have already proposed different statistical algorithms to predict the response (35).

Currently, there is considerable support for the notion that the interindividual variability in response to dietary modification is determined by genetic factors, especially for lipid and lipoprotein phenotypes (36). Indirect evidence supporting this hypothesis comes from the general observation that the phenotypic response to diet is determined partly by the baseline value of the phenotype that is itself affected by genetic factors (31). However, taking into account the complexity of lipid metabolism, the main problem is how to uncover and elucidate the many potential gene–diet interactions.

HOW NUTRIENTS COMMUNICATE WITH GENES

Before presenting some of the current nutrigenetics evidence in the area of lipid metabolism and CVD, it is helpful to gain an understanding of how nutrients and other chemicals in the diet may influence gene expression and drive those gene–diet interactions. This, in fact, is the current challenge of nutrigenomics. Past technological limitations have restricted the investigator to a piecemeal approach: one gene, one gene product, and one nutrient at a time. The current technological advances are changing the playing field. For the first time, researchers can cast a wide net in the form of microarrays that can potentially capture the information about each one of the genes expressed in a specific cell or tissue of interest. Still, despite these advances, the problem at hand is not trivial given the chemical complexity of food and our incomplete knowledge about the various bioactive components present in food.

One of the simplest events of our daily lives makes a good example: Breakfast. After waking, most people switch from the fasting to the postprandial mode, eliciting an amazing number of metabolic changes aimed at maintaining homeostasis of biological systems. A heart-healthy breakfast found in the American Heart Association cookbook might include turkey sausage patties accompanied by orange juice and coffee with milk and sugar. This simple meal contains dozens of nutrients already known to interact directly or indirectly with genes to regulate their expression (37) and this does not take into consideration the hundreds of, as yet, poorly defined bioactive substances not included in most food tables (38). To simplify the presentation of the concept, discussion here will be limited to describing how a group of dietary factors (ie, long-chain polyunsaturated fatty acids [PUFAs]) communicates its presence to genes through specific transcription factors to elicit biological responses.

The simplest mechanism for fatty acid regulation of gene transcription is for the fatty acid (or a metabolite) to bind to and regulate the activity of a transcription factor. The nuclear receptor superfamily consists of 48 mammalian transcription factors that regulate nearly all aspects of development, inflammation, and metabolism. Two subclasses, the peroxisome proliferator-activated receptors (PPARs) and liver X receptors, are lipid-sensing receptors that have critical roles in lipid and glucose metabolism (39-41). PPARs are the best-known fatty-acid–regulated

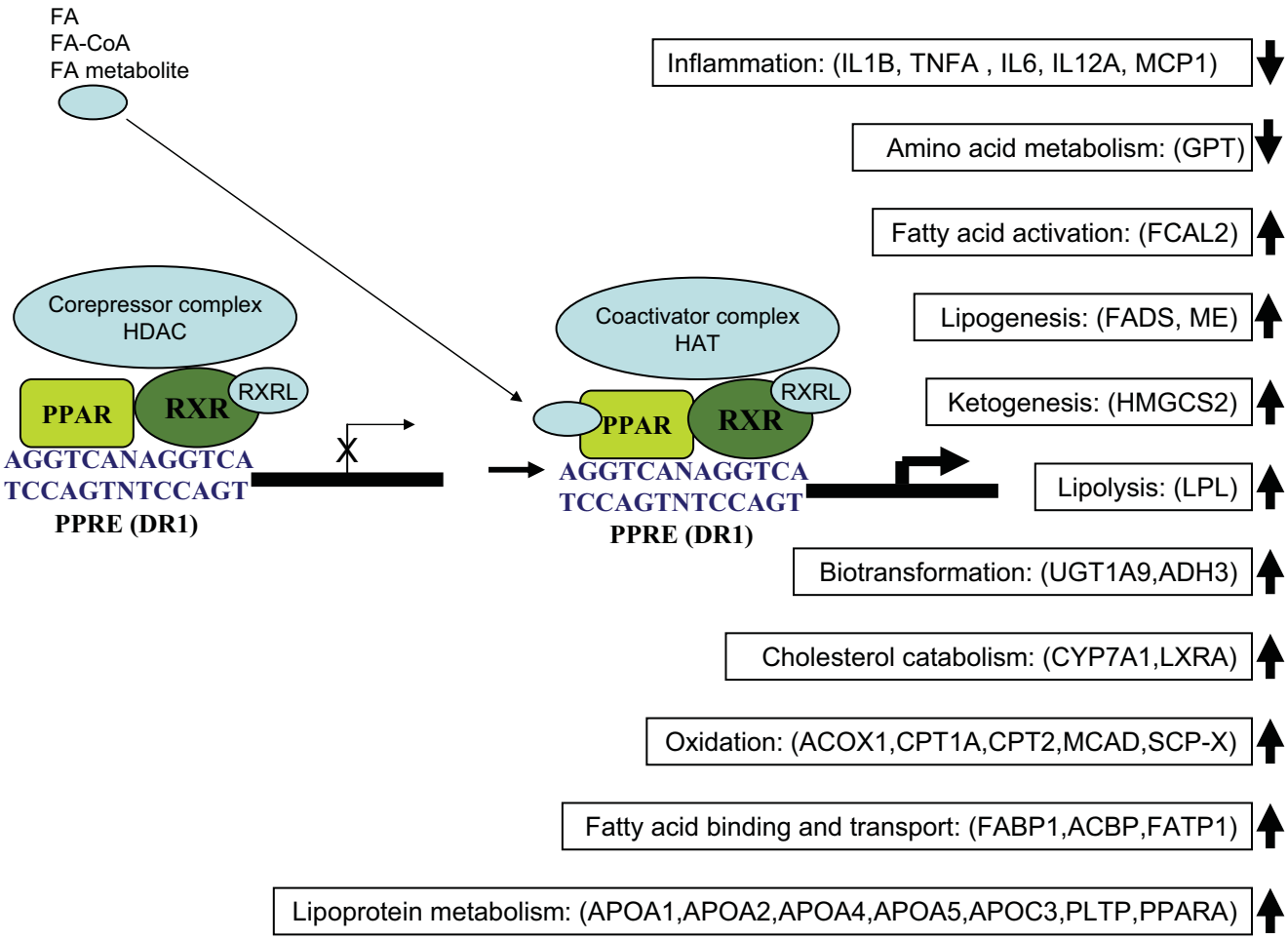

Figure. Scheme for peroxisome proliferator-activated receptor-alpha (PPARA) regulation of gene transcription. PPARA binds deoxyribonucleic acid at direct repeats (DR1) as a heterodimer with retinoid X receptor (RXR). In the unliganded state, this complex binds corepressor proteins. In the liganded state (RXRL), the corepressor complex is replaced by a coactivator complex. This conformational change initiates the exchange of proteins interacting with nuclear receptors and promotes gene activation for different metabolic pathways as shown in this representative sample. Abbreviations: FA=fatty acids. CoA=coenzyme A. HDAC=histone deacetylase. HAT=histone acetylase. PPAR=proliferator-activated receptor. PPRE=peroxisome proliferator-activated receptor response element. IL1B=interleukin 1-beta. TNFA=tumor necrosis factor-α. IL6=interleukin 6. IL12A=interleukin 12A. MCP1=monocyte chemotactic protein 1. FADS=fatty acid desaturases. ME=malic enzyme. HMGCS2=mitochondrial 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) synthase. GPT=glutamate pyruvate transaminase. FACL2=fatty acid coenzme A ligase, long-chain 2. LPL=lipoprotein lipase. UGT1A9=UDP-glycosyltransferase 1 family, polypeptide A9. ADH3=alcohol dehydrogenase 1C. CYP7A1=cytochrome P450, subfamily VIIA, polypeptide 1. LXRA=liver x receptor α. FABP1=fatty acid-binding protein 1. ACBP=acyl-coenzyme A binding protein. FATP1=fatty acid transport protein. ACOX1=acyl-coenzyme A oxidase 1. CPT1A=carnitine palmitoyltransferase I. CPT2=carnitine palmitoyltransferase II. MCAD=acyl-coenzyme A dehydrogenase, medium-chain. SCP-X=sterol carrier protein-X. APOA1=apolipoprotein A-I. APOA2=apolipoprotein A-II. APOA4=apolipoprotein A-IV. APOA5=apolipoprotein A-V. APOC3=apolipoprotein C-III. PLTP=phospholipid transfer protein.

nuclear receptors (42). After entering cells, fatty acids are likely transported to the nucleus in association with fatty-acid binding proteins, which facilitates their interaction with PPARs. Several PPAR subtypes have been described. PPAR-alpha (PPARA) plays a key role in lipid oxidation and inflammation, whereas PPAR-gamma is involved in cell (adipocyte) differentiation, glucose lipid storage, and inflammation. Finally PPAR-delta (also known as PPAR-beta), may play an important role in development, lipid metabolism, and inflammation. In addition to fatty acids, pharmacological agonists have been developed for each receptor: PPARA binds fibrates, PPAR-delta binds lipophilic carboxylic acids, and PPAR-gamma binds glitazones. The fibrates are used to treat hyperlipidemia. The glitazones are used to manage plasma glucose levels in patients with insulin resistance (43).

PPARs bind specific deoxyribonucleic acid sequences known as PPAR response elements (PPREs), which are present in the promoter regions of, probably, hundreds of genes (41,44) (see the Figure). The PPRE sequences (AGGTCA or TGACCT) are known as direct repeats, with the

spacing between the two repeats varying from receptor to receptor and from gene to gene. To date, most PPREs are direct repeats with one intervening nucleotide. Theoretically, it should be easy to find PPAR-responsive genes just by scanning their promoter regions for the consensus sequences; however, defining the boundaries of the promoter region of genes has proven challenging. Moreover, PPREs don't have a fixed position within promoters. Whereas some genes have the PPRE located one base pair from the transcription initiation site, others have been found up to 6,000 base pairs 5′ to the gene and this may not be the upper limit, as other as yet undiscovered PPREs may be positioned even farther from their respective genes.

PPARs do not act alone; they form heterodimers with the retinoid X receptor (see the Figure). As with other nuclear receptors, the binding of ligand (PUFAs or their metabolites in our example) stimulates recruitment of coregulators to the promoter. Subsequent binding of the heterodimeric PPARA-retinoid X receptor ligand-complex to the PPAR response element causes changes in gene transcription. A number of genes are induced, such as those involved with fatty-acid oxidation or fatty-acid storage, depending on the cellular metabolic state (see the Figure).

Of the three members of the PPAR family of nuclear receptors, PPARA is the one that appears to be more relevant in terms of fatty-acid–mediated activation (41,42). PPARA is highly expressed in liver, heart, and skeletal muscle, tissues that derive a high level of their energy requirements from lipids. During prolonged fasting, hypoglycemia results and fatty acids are released from fat depots and travel to the liver where they are taken up, oxidized, and metabolized into ketone bodies to provide fuel for peripheral tissues. Moreover, PPARA agonists regulate the levels of plasma lipoproteins and induce a less atherogenic lipid profile by lowering plasma triglycerides and increasing plasma HDL levels. The former action is mediated by increasing lipid uptake, activation, and catabolism through the transcriptional modulation of numerous genes that control these processes. The latter is mediated, in part, by augmenting hepatic production of apolipoprotein A-I (apoA-I) and apolipoprotein A-II, the major protein components of HDL (44).

In addition to maintaining lipid homeostasis, PPARA agonists have direct vasoprotective effects. Endothelial cells play a key role in the atherogenic process. It has been shown that PPARA agonists block cytokine-mediated induction of vascular cell adhesion molecule 1 by inhibiting the nuclear factor-kappa B signaling pathway. They also increase nitric oxide production, suggesting a protective vasodilatory effect. When vascular smooth muscle cells are cultured with PPARA activators, anti-inflammatory actions are observed, such as inhibition of cytokine-induced nuclear factor-kappa B signaling, which results in reduced expression of cyclooxygenase 2 and cytokine production. Activation of PPARA in cultured macrophages induces the expression of the HDL scavenger receptor B-I and the cholesterol transporter, adenosine triphosphate binding cassette transporter 1, thereby providing a means to augment cholesterol efflux from macrophages and promote reverse cholesterol transport (43).

This is a summary of the current understanding of the PPAR system, with most of the data deriving from animal models and in vitro studies. Now, returning to the person starting his or her day with the turkey-sausage-patties breakfast, the response to the new metabolic state (fed) will depend on how well the different components will be able to orchestrate their actions. In other words, physiological outcomes (phenotype) will reflect how polymorphisms in relevant genes influence the expected responses. In this regard, many of the previously published nutrigenetic studies focused on genes that are the subject of regulation by PPARs and other nuclear receptors (44). Therefore, it is quite plausible that polymorphisms in promoter regions that disrupt the communication with these transcription factors will have significant consequences in a person's response to dietary factors (eg, PUFAs). It is also obvious that polymorphisms within the transcription factors themselves will have a significant influence on the way that each one of us responds to dietary factors. In the following section some of this evidence is discussed.

COMMON GENETIC VARIANTS AND THEIR INTERACTION WITH DIET

The evidence for gene–diet interactions between common single nucleotide polymorphisms (SNPs) at candidate genes and dietary factors related to lipid metabolism is increasing. When interpreting the results from gene–diet interaction studies, caution is needed before applying these results to clinical practice. One of the crucial factors to consider is the meaning of a "statistically significant" result. Another is the lack of replication of initial findings. Gene–diet interactions that modulate plasma lipoprotein concentrations illustrate these types of concerns.

Results from Interventional Studies

Interventional studies in which subjects receive a controlled dietary intake provide the best approach for ascertaining true dietary intake under highly controlled conditions. However, these well-controlled feeding studies have several important logistical limitations, such as the small number of participants and the brief duration of the interventions. There are scores of interventional studies examining gene–diet interactions on different parameters of lipid metabolism. However, the level of replication among studies analyzing the same genetic variation tends to be low. Potential reasons for the lack of replication are the different characteristics of study subjects, length of intervention, sample size limitation, and heterogeneity in the design. In a systematic review (1966-2002), Masson and colleagues (45) identified 74 relevant articles, including dietary intervention studies, that had measured the lipid and lipoprotein response to diet in different genotype groups and 17 reviews on gene–diet interactions. After a comparative analysis of the individual findings, they concluded that there is evidence to suggest that variations in the apoA-I, apolipoprotein

A-IV, apolipoprotein B, and apolipoprotein E genes contribute to the heterogeneity in the lipid response to dietary intervention and that all of these genes are regulated directly or indirectly by PPARA or other nuclear receptors. However, the evidence suggested by Masson and colleagues (45) in relation to the above genes comes from meta-analyses of the published data and described the average effect. It should be noted that there is not total consistency among individual studies.

More recently, we have reviewed this topic extensively and included additional studies reported after 2002 (17-19). The median for the sample sizes included in these more recent studies is in the range of 60 subjects per study, which highlights one of the traditional problems listed above as the basis for lack of reproducibility, which is low statistical power. Moreover, it should be noted that the composition of the dietary intervention varies considerably between studies. Therefore, for future work it is desirable to standardize key variables when considering the design of interventional studies. A minimum set of variables would include patients' characteristics, medications, composition and length of the dietary treatment, and sample size. Such standardization would allow better comparison among studies and the possibility of conducting meta-analyses, which is not possible under current experimental conditions.

Results from Observational Studies

Observational studies have the advantage of large numbers of subjects and the ability to estimate long-term dietary habits. However, the level of evidence of the results obtained from these studies has traditionally been considered to be lower than that of experimental studies. Nevertheless, this level can be increased by taking into consideration the principle of Mendelian randomization (46). This concept reflects the random assortment of alleles at the time of gamete formation. Such randomization results in population distributions of genetic variants that are generally independent of behavioral and environmental factors that confound epidemiological associations between potential risk factors and disease. Again, this topic has been extensively reviewed (17-19). The median population size for recent studies is approximately 850. This sample size may be informative for traditional genotype–phenotype association studies but, considering the higher measurement error of dietary intake in comparison with experimental studies, it may not have enough statistical power to address properly the complexity of gene–environment interactions. In general, as pointed out for intervention studies, replication of results is still very low. In addition, these findings need the synergy of those studies examining the effects of nutrients on gene expression (nutrigenomics) to provide the mechanistic knowledge that will support the reported statistical associations.

Some interesting findings do begin to emerge even across experimental designs, as is the case with our discussion involving the PPARA gene. A common SNP known as PPARA L162V shows significant interactions between PUFA consumption and plasma lipoprotein levels in both observational and interventional studies (47,48). In a recent study we examined the PPARA–dietary fat interaction in relation to plasma lipid variables in a population-based study consisting of 1,003 men and 1,103 women from the Framingham cohort who were consuming their usual diets (47). We found statistically significant interactions between the L162V polymorphism of the PPARA gene and total PUFA intake, which modulated plasma TAG and apolipoprotein C-III (apoC-III) concentrations. The 162V allele was associated with greater TAG and apoC-III concentrations only in subjects consuming a low-PUFA diet (below the population mean, 6% of energy). However, when PUFA intake was high (>8% of energy), carriers of the 162V allele had lower apoC-III concentrations. This interaction was also significant when PUFA intake was considered as a continuous variable, suggesting a strong dose–response effect. When PUFA intake was <4% of energy, 162V allele carriers had approximately 28% higher plasma TAG than did 162L homozygotes. Conversely, when PUFA intake was >8% of energy, plasma TAG levels in 162V allele carriers were 4% lower than in 162L homozygotes. Similar results were obtained for n-6 and n-3 fatty acids. Our data show that the effect of the L162V polymorphism on plasma TAG and apoC-III concentrations depends on the dietary PUFA, with a high intake triggering lower TAG in carriers of the 162V allele.

Other investigators examined this PPARA L162V polymorphism using a dietary intervention approach (48) to test if plasma lipoprotein and lipid responsiveness to a modification in the dietary ratio of polyunsaturated to saturated fatty acids was influenced by this polymorphism in 10 male carriers of the V162 allele and 10 L162 homozygous men who were matched according to age and body mass index. During the intervention period all subjects followed the National Cholesterol Education Program Step I diet, but intake of polyunsaturated and saturated fatty acids was adjusted to obtain a ratio of 0.3 for the first 4-week period (low-polyunsaturated to saturated fatty acid ratio diet) and a polyunsaturated to saturated fatty acid ratio of 1.0 for the next 4-week period (high-polyunsaturated to saturated fatty acid ratio diet). After the high polyunsaturated to saturated fatty acid ratio diet, a significant gene-by-diet interaction was observed for changes in plasma total cholesterol, apoA-I, and cholesterol concentrations in small LDL particles. These results are enticing considering that apoA-I is one of the genes regulated by PPARA following activation by PUFAs.

Gene–Diet Interactions in the Postprandial State

Nowadays, human beings living in industrialized societies, due to the meal consumption patterns and the amounts of food ingested, spend most of the waking hours in a nonfasting state. Returning to the turkey-sausage-patties breakfast example, this sample individual is in what has become the normal metabolic state of the modern human being: the postprandial state. Postprandial lipemia, characterized by a rise in TAG after eating, is a dynamic, non–steady-state condition (49). More than 25 years ago, Zilversmit (50) proposed that atherogenesis was a postprandial phenomenon as postprandial lipoproteins and their remnants could deposit into the arterial wall and accumulate in atheromatous plaques. Several studies have investigated the potential interaction be-

tween some polymorphisms in candidate genes and diet on postprandial lipids (18). In postprandial studies, subjects usually receive a fat-loading test meal that has differing compositions depending on the nutrient(s) to be tested. After the test meal, blood samples are taken to measure postprandial lipids and compare with preprandial levels (49). Consistency is still very low and replication is a major need for postprandial studies because the number of subjects (usually <50) and the complexity of the designs may add even more bias than for other experimental approaches.

CONCLUSIONS

Although the current evidence from both experimental and observational nutrigenetics studies is not enough to start making specific personalized nutritional recommendations based on genetic information, there are a large number of examples of common SNPs modulating the individual response to diet as proof of concept of how gene–diet interactions can influence lipid metabolism. It is critical that these preliminary studies go through further replication and that subsequent studies be properly designed with sufficient statistical power and careful attention to phenotype and genotype. The many challenges that lay ahead are evident. This review examined the vast world of nutrigenetics and nutrigenomics only through the small keyhole of PPARA and dietary fat. Analogous to the use of the x-ray diffraction patterns 50 years ago to determine the structure of deoxyribonucleic acid, which led to today's progress in sequencing the entire human genome, these initial steps in understanding nutrigenetics will likely lead to fundamental breakthroughs that will both clarify today's mysteries and pave the way for clinical applications. We hope bringing nutrigenetics to the state of becoming a practical and useful tool will not take 50 years. However, to arrive at the point where it is possible to assess the modulation by specific SNPs of the effects of dietary interventions on lipid metabolism, well-designed, adequately powered, and adequately interpreted randomized controlled studies (or their equivalent) of greater duration than current studies are needed, with careful consideration given to which patients to include in such studies.

Moreover, research must also investigate the potential mechanisms involved in the gene–diet interactions reported by nutrigenetic studies (51). These imperative needs can be achieved only through the collaboration of experts in the different fields involved, which must include food and nutrition professionals (52).

One of the first situations in which personalized nutrition is likely to be beneficial is with patients with dyslipidemia who require special intervention with dietary treatment. It is known that these individuals will display dramatic heterogeneity in response to the currently recommended therapeutic diets and that the recommendations will need to be adjusted individually. This process could be more efficient and efficacious if the recommendations were carried out based on genetic and molecular knowledge. Moreover, adherence to dietary advice may increase when it is supported with information based on nutritional genomics and a patient believes that the advice is personalized. However, a number of important changes in the provision of health care are needed to achieve the potential benefits associated with this concept, including a teamwork approach with greater integration among physicians and registered dietitians. When more experience is gained from patients and/or individuals at high risk, these approaches could be applied toward primary prevention.

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