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THE EFFECT OF NUTRITIONAL GENOMICS ON CARDIOVASCULAR SYSTEM

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Abstract.

The idea that obesity and cardiovascular diseases together are considered for a sizable share of adult global morbidity and mortality is supported by epidemiological data. They have intricate systems in which environmental and genetic variables interact, including nutrition. As an environmental component, nutrition has a major and well-known role in managing health and preventing obesity and disorders connected to obesity, such as cardiovascular disease (CVD). Nonetheless, people with the same food pattern but obese exhibit a notable difference in CVD. This variance might be explained by the various genetic polymorphisms which gave rise to the field of nutrigenetics. The discipline known as nutritional genomics, or nutrigenetics, examines and describes gene variants linked to varying reactions to particular nutrients and links these variations to various disorders, including obesity-related cardiovascular disease (CVD). Therefore, tailored nutrition advice depending on a person's genetic background could enhance the results of a particular dietary intervention and offer a novel dietary technique to enhance health by lowering obesity and cardiovascular disease. With these suppositions, it seems reasonable to assume that understanding food and gene interactions will provide more targeted and efficacious dietary treatments in preventing obesity and CVD by nutrigenetics-based personalized nutrition. In addition to elucidating the connection between diet and gene expression and the major nutrition-related genes involved in obesity and CVD, this research seeks to provide a concise summary of the greater significant genes linked to obesity and CVD.

Key words. Nutrigenomics, cardiovascular disease nutrients, genetics, genomics, precision nutrition.

Introduction.

The study of how particular meals interact with particular genes, which raises the danger of chronic disease such as obesity and heart disease and may also cause some types of cancer, is known as the science of the effect of nutrition on genes. This helps us understand the negative and positive impact of food on our vital systems before disease occurs. Its first breakthrough was when humans discovered the genetic map in the year 2000 [1]. We know four disorders-oxidation, metabolic processes, inflammation, or psychological stress-cause most diseases. The goal of studying nutrition's impact on genes is to comprehend how food affects the first three imbalances. It also clarifies how a person's genetic composition influences how food affects their health. It is crucial to understand this effect because chronic diseases are not caused by a single genetic mutation but rather by intricate interactions between multiple genes. This requires a great degree of control over the types of genes and environmental conditions, making the research on the relationship between diet and genes more complex and difficult to predict. Recently, Numerous studies demonstrated how nutrients alter gene expression through protein synthesis, signal transduction, gene regulation, and other processes and that not everyone benefits from them similarly. Understanding how diet influences genetics has created a window of opportunity for tailored recommendations that lessen the influence of dietary-related risk factors for disease. Though "personalized nutrition," or a diet tailored to an individual's genes, is still relatively new, it is anticipated that genes will significantly influence an individual's daily dietary needs. Finding the genes that cause or are a causative factor for chronic diseases and determining the nutrients that directly affect these genes' activity while accounting for environmental factors around them are some of the challenges that research on the impact of nutrition on genes must overcome [2-5].

Coronary Cardiovascular disease is considered the most common cardiovascular disease and is closely related to the type and quantity of food. It is also hereditary and results from the accumulation of cholesterol and fats in the walls of the arteries and its formation begins Childhood when food is saturated with fat. It has causes called danger factors, like high diabetes, Blood cholesterol, smoking, age, genetics, high blood pressure, etc., Falling under the influence of stress and psychological pressure [6]. The field of nutrigenomics seeks to understand how nutrition influences metabolism and cellular function through histone modification and DNA methylation, two epigenetic processes that alter gene expression. The eicosanoid Biosynthesis insight focuses on the most recent findings about the nutrigenomics of carbs and fats to provide insight into how gene interactions and food components affect an individual's phenotype [7,8].

Recent research has provided substantial evidence of the impact of gene-diet interactions on CVD biomarkers, as well as the onset and course of the disease. Age groups and populations have shown consistent results regarding the cardiovascular implications of gene-nutrient interactions with respect to macronutrients and genes. On the other hand, the impacts of certain genes on gene-nutrient interactions have only been observed in particular age groups, genders, or populations, and they require further investigation and verification [9,10].

Heart disease is a group of illnesses that includes the following diseases: deep vein thrombosis, pulmonary embolism, peripheral

arterial, coronary heart, rheumatic heart, and cerebrovascular. With almost one-third of all deaths coming from CVD, it is the main cause of death worldwide. The USA is not far behind other low- and middle-income nations, where almost three-quarters of deaths occur. In the US, cardiovascular disease is the cause of one in four fatalities. Genetic factors largely influence cardiovascular illnesses, but there is also strong evidence linking nutrition and lifestyle variables—such as obesity and sedentary behavior—to the onset, progression, and risk factors of CVD. It is also well recognized that a person's nutrition and lifestyle choices throughout their early years can impact their later-life risk of illness. People have long been fascinated by the differences in CVD susceptibility among genotypes, ethnicities, and environments. Recently, there has been a surge of curiosity regarding the impact of individual genetic variation on how human populations respond to nutrition. Additionally, there is a growing understanding that combining genes and environment, such as diet and nutrition, can significantly influence metabolic changes. Thus, one of the most important aspects of controlling CVD is comprehending the basic mechanisms behind the disease and putting this information to use [11-15].

Finding genetic variants that affect the risk of CVD due to food may help guide future research on nutritional interventions. Even though a wealth of scientific data shows that nutrition can alter a person's hereditary vulnerability to cardiovascular disease, diet recommendations are still difficult to implement based on this knowledge. Therefore, Better methods are required to obtain accuracy in gathering dietary data and to simplify computational methods for significant and successful nutritional treatments [16].

Researching the impacts of dietary patterns and specific nutrients has attracted much interest. Many dietary strategies, such as Mediterranean, Prudent, and Dietary Approaches to Stop Hypertension (DASH), are good for cardiovascular health. They all stress the health benefits of fruits, vegetables, and whole grains and the negative consequences of sweets, saturated fats, and sodium. The trial is a well-known study that illustrates the advantages of the Mediterranean diet. The PREDIMED experiment aimed to ascertain how different types of fat affected the mortality rate from CVD. High-risk Spanish adults for cardiovascular reasons are following a low-fat or Mediterranean diet supplemented with almonds or olive oil. Providing nuts or olive oil along with instructions was the foundation of the intervention. The rate of significant CV events served as the main outcome. According to Ortega-Azorin and colleagues, a low Mediterranean diet was associated with a higher relationship between FTO-rs9939609 MC4R-rs17782313 and T2D [17-19]. Several PREDIMED trial studies have shown how well a Mediterranean diet can modulate the genetic associations that lead to diabetes, obesity, and other cardiovascular disease risk factors. A multi-center study, Dietary Approaches to Stop Hypertension (DASH), examined how healthy eating habits could affect hypertension. An analysis of genotype differences in the angiotensinogen, beta2-adrenergic receptor, and kallikrein loci revealed differences in the effects of sodium intake on blood pressure between persons following the Western diet and the DASH diet. Furthermore, the combination of low-fat and hypocaloric diets interacts with BDNF SNPs and circadian locomotor cycles kaput (CLOCK) to influence phenotypes related to obesity, inflammation, and diabetes (Table 1) [20].

The relationship of some foods to diseases.

In countries with good statistical coverage, it was found that in more than 30% of cases, food contributes to diseases such as cancers and other physiological diseases, including atherosclerosis, obesity, high blood pressure, and diabetes (especially type 2). There are also a number of diseases that were known in the past and were treated by modifying food intake, such as scurvy, which results from a deficiency of vitamin C and has its well-known characteristics and symptoms, and its severity increases when it occurs in early childhood, represented by a disturbance in the growth of muscles and connective tissues. It was possible to get rid of this defect by increasing the intake of foods containing On vitamin C or using pharmaceutical preparations, as well as beriberi disease resulting from a deficiency (vitamin B1) Thiamine, which leads to symptoms mainly concentrated in dysfunction of the nervous system, heart disease, etc., as well as rickets resulting from a deficiency of vitamin D, which can be inherited and passed on to generations. The next in addition to other diseases, the most important of which are chronic conditions, some of which can be summarized in (Table 2) [21].

Obesity and cardiovascular diseases (CVDs).

The extensive deterioration of cardiovascular physiology resulting from structural and functional changes generated by obesity is one of the most significant effects of obesity. Due to increased blood volume, cardiac output, stroke volume, and heart rate, these adaptive mechanisms translate into significant hemodynamic changes that lead to progressive cardiac remodeling, including left atrial enlargement, left ventricular (LV) dilation, and eccentric or concentric LV hypertrophy. The effects of extra adipose tissue on the body have been well-documented. These effects include the synthesis and release of hormones and cytokines. Adipokines are among the latter, and they play a key role in several pathways leading to chronic low-grade inflammation formation. This inflammation raises the danger of developing heart disease (HD) because of its proatherogenic action. The accumulation of extra adipose tissue increases the deposition of epicardial adipose tissue (EAT), which is known as a critical factor in developing obesity-related cardiovascular problems. A local proatherogenic impact caused by elevated EAT raises the risk of arrhythmias, such as atrial fibrillation and coronary heart disease. Changes in the gut microbiota brought on by obesity set off several inflammatory cascades that raise the risk of cardiometabolic events and the generation of metabolites linked to cardiovascular risk. The microbiota-derived metabolite trimethylamine N-oxide, identified as a predictive marker for obesity-related cardiovascular events beyond conventional danger factors, has come to light due to emerging evidence. Specifically, research has shown that TMAO increases the danger of heart failure, stroke, and atherosclerosis. A recent study found that TMAO serum levels positively correlated with the Fatty Liver Index and the Visceral Adiposity Index, serving as a gender-specific predictor of non-alcoholic fatty liver problems and an indicator of adipose dysfunction, respectively [22-25].

Results and discussion

Table 1. *Gene by nutrition interaction impacts on CVD biomarkers that are consistent (replicated).*

Gene	SNP	Nutrient/diet	CVD outcome	Discussion
ACE	rs4343	Blood pressure	-	Compared to AA or AG carriers, GG carriers exhibited greater systolic blood pressure.
ACE	INDEL	Hypertension	-	In ID/DD genotype but not II genotype, a higher salt intake was associated with an increase in hypertension.
CLOCK	rs4580704	Mediterranean diet	Type 2 diabetes status	After approximately five years of intervention, G carriers had a lower risk of type 2 diabetes than CC genotypes.
CLOCK	rs4580704	Low fat diet	C-reactive protein	After a 12-month intervention, CC carriers had a higher reduction in hs-CRP than CG or GG carriers.
CLOCK	rs1801260	Low fat diet	Insulin concentrations	After a year of intervention, TT carriers showed greater insulin sensitivity, lower plasma insulin, and HOMAIR than C carriers.
CLOCK	rs3749474	Hypocaloric diet	BMI	When dietary fat rose, T carriers' BMI increased, but following a 84 days calorie restriction program, CC carriers' BMI did not alter.
FTO	rs8050136	Carbohydrate intake	Obesity	In a cross-sectional study of Asian Indians, carriers of A had a higher risk of obesity than carriers of CC.
FTO	rs9939609	High protein intake	BMI	In children who consumed more protein, there was a larger correlation between BMI and rs9939609.
FTO	rs1558902	Protein intake	BMI	AA carriers who consumed less protein than TT carriers did so at a greater BMI.
FTO	rs9939609	Protein intake	BMI	When comparing the low-protein consumption group to the high-protein intake group, the association between rs9939609 and BMI was less pronounced.
FTO	rs9939609	Dietary saturated fat intake	Obesity	Compared to TT carriers, A carriers had a greater risk of obesity that was increased by a high intake of saturated fat in the diet during the course of a 7.5-year longitudinal study.
FTO	rs9939609	Energy-adjusted fat intake	BMI	In the high-fat diet group, but not in the low-fat diet group, carriers had greater BMI consumption.
FTO	rs1558902	Fried food consumption	BMI	Compared to low or normal fried food users, there was a higher correlation between the FTO variant and BMI in high fried food consumers.
BDNF	rs4923461	High protein intake	BMI	Compared to GG carriers, A carriers had a higher BMI and consumed more protein.
BDNF	rs10767664	Hypocaloric diet	BMI	After 90 days intervention, obese participants with AA carriers exhibited a higher reduction in BMI than those with T carriers.
FADS1	rs174547	Linoleic acid (LA) intake	BMI	Instead of the high LA intake group, each copy of the minor allele was linked to a reduced waist circumference and BMI in the lower LA intake group
FADS1	rs174547	Polyunsaturated fat (PUFA) intake	LDLc	In a cross-sectional investigation, C carriers compared to TT carriers showed reduced LD values only in the lowest tertile of n-3 PUFA intakes.

BDNF, or brain-derived neurotrophic factor; ACE, or angiotensin-converting enzyme; Kaput is cycled by the CLOCK Circadian Locomotor Output; FTO Fat mass and obesity-associated BMI Body mass index; FADS1 fatty acid desaturase 1; Lower-density lipoprotein cholesterol, or LDLc.

Table 2. *The relationship of some foods to diseases.*

	Diseases			
Food type	**Cancers**	**Arteriosclerosis**	**Obesity**	**diabetic**
Foods rich in calories	+	+	+	+
Foods rich in saturated fats	+	+	+	+
High salty foods	+ **	+	...	+
Foods poor in fiber and complex carbohydrates	+	+	...	+
Foods poor in antioxidants	+	+	...	+

+ Having a huge impact.
*** Helped by the presence of other foods.*
...No effect detected.

Nutrition Aspects of prohibition in cases of fatness.

Research conducted on the matter has shown that nutrition and lifestyle significantly impact CVD risk. This is why public health programs to lower the risk of CVD have focused on dietary guidelines. Despite that effort, the anticipated decrease in CVD mortality only sometimes materializes. This failure is marked as a genetic variation and individual variability in response to dietary recommendations and potentially to the reciprocal interactions between both factors [26-28].

The Human Genome Project identified numerous genes and the proteins that result from them as potentially contributing to these variations in how differently people respond to nutrition. The field of study known as "nutrigenetics" examines how genetic variability controls how differently each person reacts

to a given diet. It can be viewed as a subset of nutrigenomics, which more broadly studies how foods interact with the genome while accounting for genetics, epigenetics, and variations in gene expression. Advances in nutrigenomics and nutrigenetics have made it possible to use tailored nutrition to prevent serious illnesses like cardiovascular disease (CVD). According to epidemiologic studies, individual genetics play a major role in the significant tendency to CVD. Several twin and familial investigations and extensive long-term cardiovascular cohort studies validated this idea. Numerous genes or loci linked to atherosclerosis were found by GWAS; other studies have validated several of these findings [29,30].

Nevertheless, the found susceptibility alleles could only account for approximately 30% of the predicted heritability variance. Several limitations of genetics research have been proposed as contributing to the missing heritability, including the failure to take gene–gene interactions into account, the study power being inadequate to identify rare variants, and the role of environmental factors, such as dietary habits, among others. With these suppositions, it makes sense that clarifying gene-diet connections will facilitate more targeted and efficient tailored nutrition therapies for CVD prevention. Cardiovascular events may be avoided by adopting nutrigenetics, which focuses on genetic variations that can explain differences in how different nutrients and dietary treatments affect an individual. As was previously indicated, several studies demonstrated that, depending on the many dietary components contained, there is a significant variation in response to dietary intervention. Molecular genetics was investigated as soon as it was discovered as a tool capable of explaining this variability. However, dietary reference values—like recommended dietary allowances are created assuming that the various metabolic outcomes resulting from nutrient intake follow a Gaussian distribution and are intended for the whole population. Because population subgroups have different genetic makeups, these reference values may not be optimum for them. For example, there may be considerable differences in transferring the proteins for a given vitamin or in the activity of enzymes needed to metabolize that micronutrient or require it as a cofactor. While a single SNP might not have much impact compared to other established risk factors (like a family history of CVDs), several tiny genetic variations linked to different environmental exposures (like an unsatisfactory diet) may cause significant alterations in gene expression. The interactions between these variables may significantly alter the final phenotype or, conversely, may be in danger due to the co-existence of these adverse circumstances. This context may be especially concerning when it comes to pathways that may encourage atherogenesis (i.e., inflammation and lipid metabolisms) in individuals with high cardiovascular disease risk, such as obese people [31-35].

In the early years of this field, most nutrigenetic studies were observational; however, in the last few years, there has been a notable surge in the number of interventional studies, including genetic variability for dietary responsiveness. This is significant since one of the most common criticisms against nutrigenetics and nutrigenomics by skeptics was that observational rather than interventional research was used to derive treatment recommendations based on molecular nutrition. In this regard, new data from nutrigenetics-based interventional research has shown some pathways that may be responsible for a variety of dietary responses and, as a result, may either cause or prevent CVD in patients who are at risk [36].

Genetic variations influencing a patient's response to a nutritional intervention designed to lower their risk of cardiovascular disease.

The genetic contributions to pathways that should be taken into account when creating individualized dietary recommendations to prevent cardiovascular disease in obese people are described in the paragraph that follows. Here, we present new data that supports the link between certain food intake responsiveness and genetic variations. To find uses for nutrigenetics in clinical practice, we specifically concentrated on observational research and clinical trials (summarized in Table 1) examining the impact of nutrient supplementation on cardiovascular outcomes. Figure 1 [20], reports a graphic representation of individualized therapies designed to lower the risk of cardiovascular disease (CVD) in obese patients based on how well they respond to particular nutrients or dietary regimens.

Graphical depiction of individualized interventions designed to lower the risk of cardiovascular disease (CVD) in obese patients based on how well they respond to particular nutrients or diets. In obese patients, a customized diet based on nutrigenomics can prevent cardiovascular disease by improving lipid profiles and reducing inflammation [37].

Folate.

Micronutrient abundance and shortage are well known to affect the stability of the genome, which in turn affects nutrient and gene–nutrient interactions (which are impacted by genotype). SNPs can affect the level of micronutrients and their associated metabolic disorders. Consequently, by controlling these interactions, (micro)nutrients may raise or lower the likelihood that a disease would manifest [38].

The control of homocysteine levels through folate intake is a key example. An integrated indicator of one-carbon metabolism, plasma homocysteine is positively connected with alcohol intake and negatively correlated with folate, vitamin B6, and vitamin B12 intake. One indicator of the risk of CVD is the build-up of homocysteine. Inflammation is one of the many pathways that have been proposed to encourage the beginning of CVD. The estimated heritability of plasma homocysteine is 8–57%. Among the most studied variants linked to elevated plasma homocysteine is the 5,10 MTHFR gene's C677T polymorphism (rs1801133). Because carriers of the T allele have a decreased capacity to convert methylenetetrahydrofolate to methyl-tetrahydrofolate, the one-carbon cycle pathway's homeostasis is compromised. According to a recent meta-analysis, the TT genotype has been linked to reduced blood folate levels, higher plasma homocysteine levels, and a decreased response to short-term folate supplementation. These findings reinforce the necessity of identifying MTHFR TT carriers to minimize negative consequences and guarantee that sufficient folate consumption can overcome genetic factors that may raise the risk of developing CVD. It has been shown that the MTHFR genotype affects how well hyperhomocysteinemia is treated with folate supplementation [39,40].

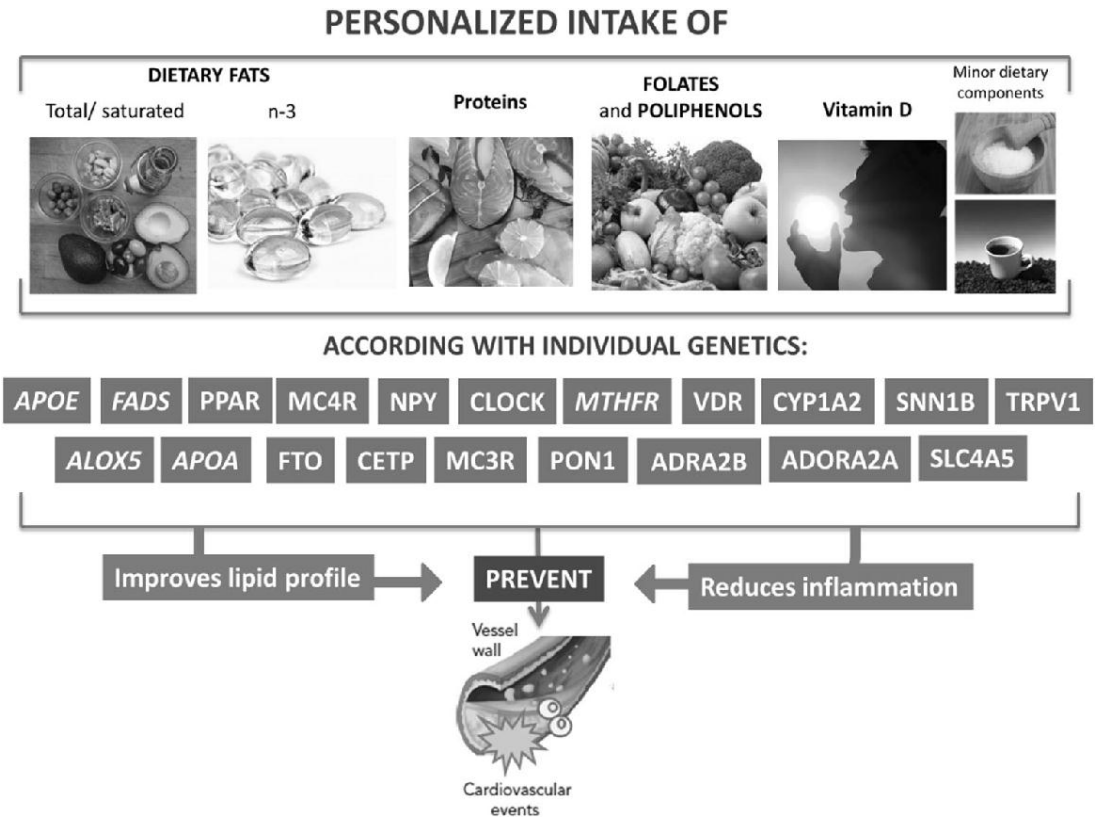

Figure 1. *Nutrition tailored by nutrigenetics for obesity and cardiovascular disorders. Graphical depiction of individualized interventions designed to lower the risk of cardiovascular disease (CVD) in obese patients based on how well they respond to particular nutrients or diets. In obese patients, a customized diet based on nutrigenomics can prevent cardiovascular disease by improving lipid profiles and reducing inflammation[37].*

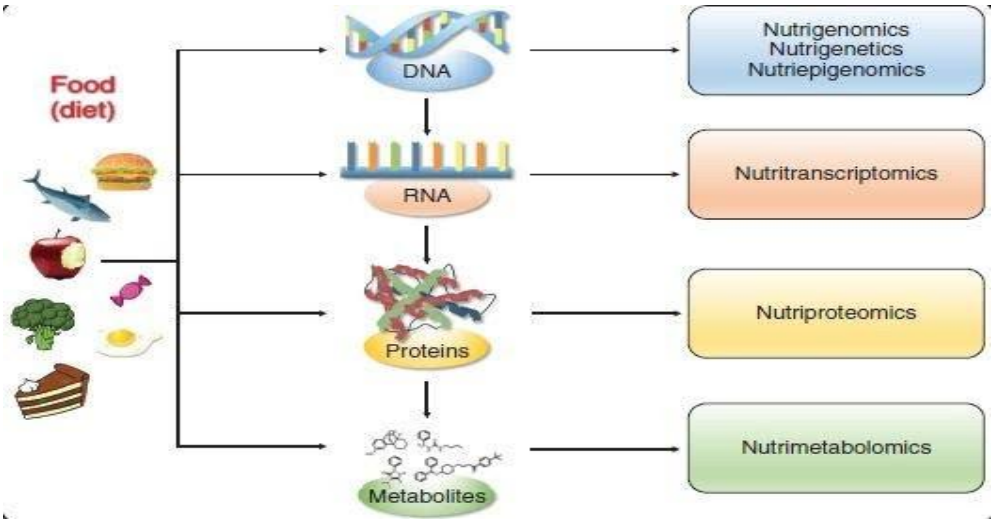

Figure 2. *Results of OMICs and their impact on nutritional studies.*

Carbohydrate nutrition and its genetic effects.

Feeding a high-energy diet causes obesity and metabolic syndrome to develop early in life, perhaps because the body is unable to handle the meal's high energy density. Type 2 Diabetes, Obesity, and Energy Balance. In this situation, glucose is the ideal illustration of how organisms can adapt to varying dietary availability. Mammals have a complex response to dietary glucose because it involves changes in hormone production that are dependent on glucose and impact glucose metabolism, such as stimulating insulin secretion and inhibiting glucagon release. It was previously believed that glucagon and insulin were the primary up-and-down transcriptional regulators of macronutrient metabolism (Figure 2) [21].

This conventional perspective is superseded by the novel idea that glucose produces signals in cells. In addition to influencing the expression of the β-cell gene in the pancreas, glucose also affects other areas of the human body, encouraging bloodstream absorption, intracellular metabolism, and fat absorption. Glucose in adipose tissue and liver induces the transcription of glycolytic and lipogenic enzymes. Furthermore, when insulin is

present, glucose represses genes that encode for gluconeogenic pathway enzymes [41,42].

Notably, the activity of glucokinase, which initiates glucose signaling, is necessary for the liver's effective glucose-mediated control of gene transcription. Several transcription factors must be activated and induced for glucose transcriptional activity to occur. These transcription factors can all be efficiently upregulated by high-carb diets. Most of the elements that have been studied are the carbohydrate activity element-binding protein (ChREBP), which interacts with Mlx after a heterodimerization and binding procedure to the carbohydrate activity element (ChoRE) stimulating genes that are regulated by glucose, and are involved in fat synthesis, fructose degradation, and glycolysis. Colon, muscle, liver, pancreas, and adipose tissue contain high percentages of ChREBP containing a basic helix-loop/leucine loop (bHLH/ZIP) DNA-binding domain, its extensions are proline-rich, its ZIP-like domain, and its nuclear localization signal is repressed by Ser196 phosphorylation as well as by Protein kinase (PK).), and that the activation process is two-step and includes dephosphorylation of some residues involved in the first mechanism, and glucose is regulated through ChREBP. (Figures 2 and 3) [21]. This second one, however, is triggered by two regulatory domains and entails a dynamic intramolecular inhibition. A high-carb diet causes mRNA levels to rise, whereas a high-fat diet does not cause them to do so. Fasting and feeding conditions control liver ChREBP expression and activity. As a result of Thr666 in the DNA-binding domain being dephosphorylated, feeding causes ChREBP to translocate to the nucleus and activate ChREBP. A halt signal is represented by enhanced lipogenesis because it triggers AMP-activated. Stimulating lipogenesis is a stop signal because it triggers AMP-activated protein kinase (AMPK), which phosphorylates Ser568 to block ChREBP DNA-binding ability (Figure 3) [21]. In hepatic cells, the regulation of glycolytic and lipogenic genes is glucose dependent. The red-colored enzymes are those whose gene transcription is elevated in response to glucose. For more information, see the text. Rather, they demonstrated the critical role of glucose-6-phosphate (G6P) in ChREBP activation through an allosteric conformational shift that permits Mlx recruitment. Furthermore, they revealed that fructose 2,6-bisphosphate (F2,6BP) is

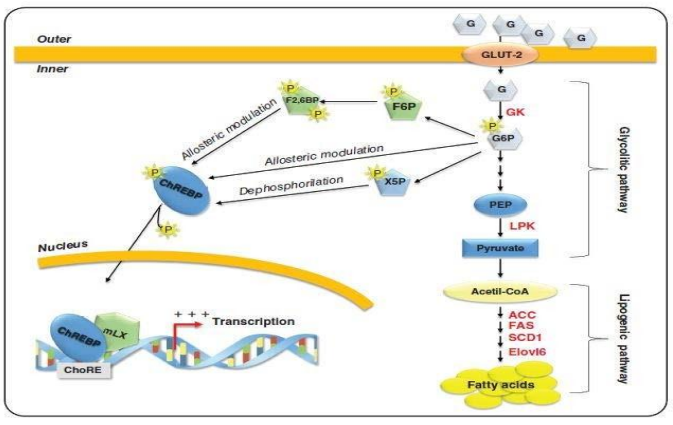

Figure 3. *Phosphorylates Ser568 to block ChREBP DNA-binding ability.*

necessary for the transcription of genes controlled by glucose in the liver; specifically, F2,6BP facilitates the recruitment of ChREBP to the promoter of target genes, such as the one encoding glucose-6-phosphatase. A concept like this does not rule out the possibility of other metabolites operating in tandem or at downstream locations. Evidence suggests that ChREBP is also involved in converting carbohydrates to lipids. For example, the livers of ChREBP/mice have lower levels of glycogen and triglycerides than those of their wild-type littermates; in obese mice, ChREBP knockdown improves insulin resistance, glucose intolerance, and liver steatosis; and in diabetic livers, ChREBP is significantly upregulated, as well as in models of hyperphagia, such as ob/ob mice [43-44].

Obese persons have higher levels of the hormone FGF-21 than lean subjects. Starvation can also produce FGF-21 through the peroxisome proliferator-activated receptor (PPAR)α. As sucrose, fructose, and glucose are also ingested, studies have linked the intake of high-sucrose diets to specific cancer onsets [45]. The mechanisms behind these effects include the expression of at least 109 genes (related to cell adhesion, metabolic pathways, cell cycle regulation, and transduction signaling) being modulated in a sucrose-dependent manner. Specifically, high-sucrose supplementation modifies genes implicated in IGF-I signaling, indicating a role for this pathway in intestinal cell proliferation dependent on high-sucrose consumption.

Lipids' Effects on Gene Expression.

Fatty acids, cholesterol, and liposoluble vitamins are examples of dietary lipids essential for healthy growth, development, and wellbeing maintenance. Similar to how dietary fats and carbohydrates affect gene expression, they do so due to a conflict with our slowly evolving genome, which is linked to several "typically Western" disorders [46].

The relationship of diet to genetic change in humans.

Epidemiological research has shown that trans fats (produced during the processing of vegetable oils) and saturated fatty acids (SFAs) are linked to a higher risk of type 2 diabetes, cardiovascular disease, and non-alcoholic fatty liver disease, which is characterized by the buildup of liver fat, insulin resistance, and metabolic syndrome. Therefore, consuming fewer saturated fats (SFAs) and more monounsaturated and polyunsaturated fats is advised to promote well-being acids (PUFAs) [47].

Through transcription factors' direct and indirect activation, dietary lipids control gene expression, affecting inflammation, endothelial functions, metabolism, and cell development and differentiation. This is the situation with polyunsaturated fats (PUFAs), which comprise the □-3 and □-6 families of PUFAs respectively. PUFAs, in particular, act as fuel partitioners, directing fatty acids away from triglyceride synthesis and absorption, towards β-oxidation and glucose towards glycogen storage. Table 1 illustrates how PUFAs, in particular N-3 PUFAs, stimulate the transcription of genes encoding enzymes for β-oxidation and thermogenesis while suppressing the transcription of lipogenic genes. Furthermore, the expression of genes linked to adipocyte development is downregulated by □-3 PUFAs and upregulated by □-6 PUFAs [48].

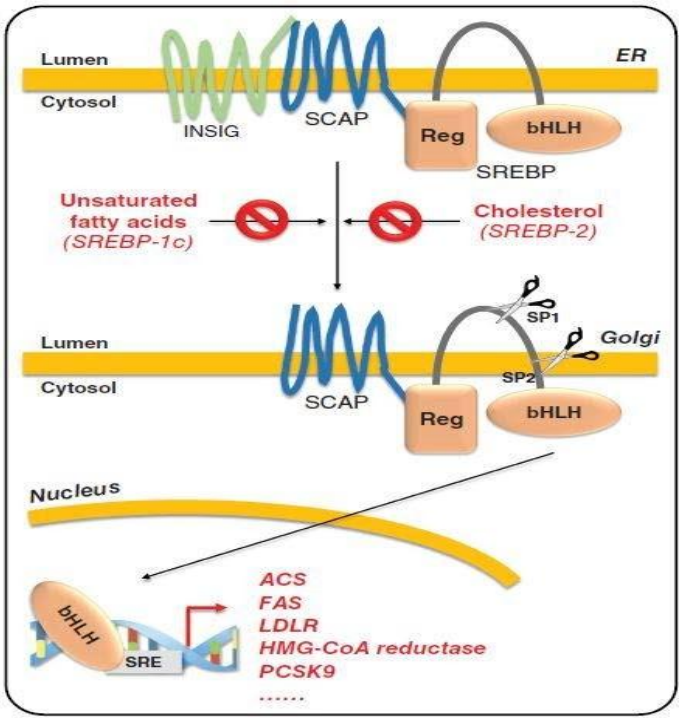

Figure 4. *Cholesterol and unsaturated fatty acids activate SREBPs by proteolysis. Refer to the text for further details. HMG-CoA, 5-hydroxy-3-methylglutaryl-coenzyme A; INSIG, insulin-induced protein; LDLR, low-density lipoprotein receptor; ER, endoplasmic reticulum; FAS, fatty acid synthase; bHLH stands for basic helix-loop-helix domain; ACS stands for acetyl-CoA synthetase; PCSK9, proprotein convertase subtilisin/kexin type 9; Reg, regulatory domain; SP1, site-1 protease; SP2, site-2 protease; SCAP, SREBP cleavage-activating protein; Sterol-responsive elements are referred to as SREs, and the protein that binds to these elements is known as SREBP.*

Fatty acids directly bind liver X receptors (LXRs) and PPARs to produce these effects. In addition, they indirectly influence the activity of other nuclear factors, such as nuclear factor kappa B (NF□B), SREBPs, and hepatocyte nuclear factor 4α (HNF4α). We outline the primary features of these receptors here, with references to additional articles for more information.

Regulation of transcription factors and their relationship to dietary fat.

Via the modulation of their regulatory pathways, fatty acids, particularly polyunsaturated fats (PUFAs), can control the quantity of certain transcription factors within the nucleus. This is an example of how both □-3 and □-6 PUFAs antagonistically activate the activator protein (AP)-1 transcription factor through a method that depends on PKC-α activation. For example, a diet high in □-6 PUFAs stimulates PKCβII activity, normally controlled by □-3 PUFAs, increasing colon cancer cell proliferation [49].

All three SREBPs have a central region with two hydrophobic transmembrane segments facing into the endoplasmic reticulum (ER) lumen, an N-terminal bHLH/ZIPDNA-binding domain, and a C-terminal regulatory domain that is found in the cytosol and is essential for SREBP maturation. Their susceptibilities to insulin, PUFAs, and cholesterol control vary, although having the same structure (Figure 4) [21].

Genetic changes and their relationship to protein nutrition.

Given the abundance of information available on protein genomics (and the nutrigenomics of micronutrients; refer to the following paragraph), a select few noteworthy instances will be discussed to illustrate the intricate web that underlies the health benefits of these nutrients [51,52].

The synthesis of cholesterol is one of the metabolic processes that dietary proteins control. Indeed, a substantial hypocholesterolemic effect (a decrease in blood total and LDL-cholesterol concentrations) is observed in proteins, particularly soy proteins, probably due to SREBP-2 regulation. As a result, giving a low-protein meal causes insulin levels to drop. It decreases the mass of pancreatic β-cells. Specifically, protein restriction hinders the function of both calcium- and cAMP-dependent PKC and PKA, which work together to cause the transcription of genes needed for insulin synthesis, glucose sensing, exocytosis, and β-cell survival that is dependent on the response element-binding (CREB) protein [53,54].

Genetic changes and their relationship to nutrients.

Minerals and vitamins are necessary nutrients that directly impact biochemical processes and can control gene expression. They enhance health by altering certain signal transduction pathways directly through interactions with transcription factors (such as vitamins A and D) or indirectly through epigenetic alterations of target promoters.

All-trans and 9-cis retinoic acid, metabolites of vitamin A, have various pleiotropic effects, including differentiation, cell death, proliferation, and metabolism. They are very important for developing embryos and fetuses and preserving the completely differentiated condition of adults. Binding to two kinds of nuclear receptors—retinoic acid, and retinoid-X, receptors—is necessary for retinoids to function. These receptors form heterodimers and bind to retinoic acid response elements (RAREs) on target gene loci [55].

Comparably, most of vitamin D's physiological effects come from attaching to the vitamin D receptor, which controls over 1000 genes throughout all tissues. However, vitamin D also causes epigenetic changes, including hypomethylation, which activates the osteocalcin promoter. By altering the redox status of transcription factors and signaling molecules, antioxidant vitamins C and E have been demonstrated to influence the production of extracellular matrix components and proteins involved in advancing the cell cycle.

Nutrients involved in one-carbon metabolism provide another interesting example. Epigenetic patterns can be modified by vitamins, certain amino acids, and certain minerals by varying the amounts of the methyl donor S-adenosylmethionine, which is required for DNA methylation and histone modifications [56,57].

Conclusion.

There is no denying that research on dietary genetics and its application to preventing and treating cardiovascular illnesses is still in its early stages. However, obtaining consistent results was greatly aided by introducing more productive (and less expensive) technologies and the increasing number of intervention studies, which included nutritional analysis. Co-

applying additional "omics" disciplines, such as transcriptomics, proteomics, metabolomics, nutritional genomics, genomes, and lipidomics, can further improve this encouraging situation. The capacity to effectively apply an integrated modeling strategy, incorporating phenotypic, genetic, and epigenetic data from the Framingham Heart research, to simulate the symptoms of coronary heart disease. This is an all-encompassing strategy for making customized drugs and diets a reality, particularly in preventing obesity and cardiovascular disease.

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