Nutrigenetics and Nutrigenomics

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ISNN Consensus Article

Guide for Current Nutrigenetic, Nutrigenomic, and Nutriepigenetic Approaches for Precision Nutrition Involving the Prevention and Management of Chronic Diseases Associated with Obesity

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Abstract
Chronic diseases, including obesity, are major causes of morbidity and mortality in most countries. The adverse impacts of obesity and associated comorbidities on health remain a major concern due to the lack of effective interventions for prevention and management. Precision nutrition is an emerging therapeutic approach that takes into account an individual's genetic and epigenetic information, as well as age, gender, or particular physiopathological status. Advances in genomic sciences are contributing to a better understanding of the role of genetic variants and epigenetic signatures as well as gene expression patterns in the development of diverse chronic conditions, and how they may modify therapeutic responses. This knowledge has led to the search for genetic and epigenetic biomarkers to predict the risk of developing chronic diseases and personalizing their prevention and treatment. Additionally, original nutritional interventions based on nutrients and bioactive dietary compounds that can modify epigenetic marks and gene expression have been implemented. Although caution must be exercised, these scientific insights are paving the way for the design of innovative strategies for the control of chronic diseases accompanying obesity. This document provides a number of examples of the huge potential of understanding nutrigenetic, nutrigenomic, and nutriepigenetic roles in precision nutrition.

Introduction

Obesity is a global epidemic with more than 35% of the world population (2,100 million people) being estimated as either overweight or obese according to body mass index (BMI) [1]. Obesity is associated with a large number of health problems including dyslipidemias, cardiovascular diseases (CVD), type 2 diabetes mellitus (T2DM), non-alcoholic fatty liver disease (NAFLD), and some types of cancer, with important economic and social costs [2]. Systematic analyses have revealed that obesity and overweight caused 3.4 million deaths in 2010 [3].

The long-term consumption of unbalanced diets (high content of calories, fat, fructose and high omega-6/omega-3 fatty acid ratio), coupled with the adoption of a sedentary lifestyle, contributes to the development of obesity and associated complications [4, 5]. Also, it is now recognized that interactions of genetic and epigenetic signatures with environmental factors (dietary intake or physical activity) play an important role in determining individual phenotypes [6, 7]. Recent advances in genomic sequencing and large cohort studies are enabling clarification of the involvement and the interplay of these factors in chronic disorders including obesity, which open a new field to customize intervention strategies [8, 9]. Precision medicine refers to disease therapeutics based on interindividual differences, such as genetic profile, phenotype, gender, microbiome, and environmental features [10]. In this context, precision nutrition is an important part of precision medicine that may aid in establishing nutritional guidelines for specific subgroups instead of conventional population-based advice [11].

Herein, we review genetic and epigenetic biomarkers related to obesity, dyslipidemia, T2DM, CVD, NAFLD, and some types of cancer that may serve to understand disease etiology and outline future therapeutic targets and treatments. In this sense, responses to dietary interventions, mainly aimed at weight reduction and management of metabolic disorders

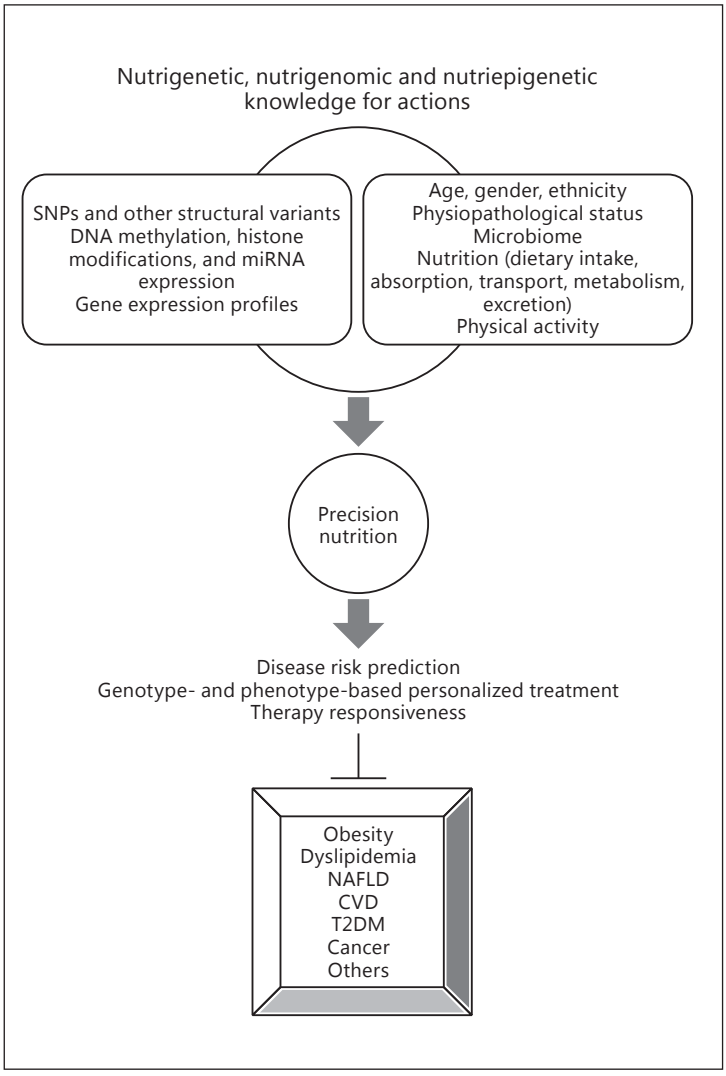

Fig. 1. Nutrigenetic, nutrigenomic, and nutriepigenetic approaches for precision nutrition to the prevention and management of obesity and associated chronic diseases.

(i.e., insulin resistance, dyslipidemias, fatty liver), are screened for their interaction with genetic and epigenetic features. Also, nutritional interventions based on certain specific nutrients and bioactive dietary compounds that can modify epigenetic marks and gene expression are reviewed. The integration of the emerging knowledge derived from different genetic and epigenetic approaches is required in order to outline new therapeutic tools for advancing in the prevention and personalized management of chronic diseases through precision nutrition (Fig. 1).

Genetic Background and Nutritional Prescriptions

International genome projects using whole-genome sequencing analyses have provided a comprehensive description of genetic variations across the human genome including single nucleotide polymorphisms (SNPs), copy number variations (CNVs), and other structural variants [12]. In recent years, nutrigenetic studies have allowed the identification of genetic variants associated with disease susceptibility through interaction with dietary factors [13].

Table 1. Nutrigenetic examples of SNPs-diet interactions involved in disease risk

Genes	Polymorphisms	Alleles	Diet interactions	Putative disease risks	Ref.
TAS1R2	rs35874116	G	High carbohydrate	Hypertriglyceridemia	[16]
CD36	rs1761667	A	High fat, SFA	Hypercholesterolemia	[17]
MTHFR	rs1801133	T	Low folate, vitamin B_6, and vitamin B_{12}	Breast cancer	[18]
MTR	rs1805087	G	Low folate, vitamin B_6, and vitamin B_{12}	Breast cancer	[18]
VDR	rs1544410	A	Low calcium	Osteoporosis	[22]
APOC3	rs5128	C	Western dietary pattern	Metabolic syndrome	[23]
APOA1	rs670, rs5069	A, T	Western dietary pattern	Metabolic syndrome	[24]
CYP1A2	rs762551	C	Moderate and heavy coffee drink	Hypertension, CVD	[25, 26]
FTO	rs9939609	T	Low adherence to Mediterranean diet	T2DM	[106]
MC4R	rs17782313	T	Low adherence to Mediterranean diet	T2DM	[106]
FTO	rs9939609	A	High fat	Obesity	[107, 108]
FTO	rs8050136	A	High carbohydrate	Obesity	[109]
MC4R	rs12970134	A	Western dietary pattern and high SFA	Metabolic syndrome	[110]
APOB	rs512535	G	High fat	Metabolic syndrome	[111]
TCF7L2	rs7903146	T	High dessert and milk	T2DM	[112]
TCF7L2	rs7903146	T	High SFA	Metabolic syndrome	[113]
LCT	rs4988235	T	High dairy products	Obesity	[114]
PPARG	rs1801282	G	High fat	Obesity	[115]
PNPLA3	rs739409	G	High carbohydrate	NAFLD	[116]
TXN	rs2301241	T	Low vitamin E	Abdominal obesity	[117]

MTHFR, methylenetetrahydrofolate reductase; *MTR*, methionine synthase; *FTO*, fat mass and obesity associated; *MC4R*, melanocortin 4 receptor; *APOC3*, apolipoprotein C3; *APOA1*, apolipoprotein A1; *APOB*, apolipoprotein B; *CD36*, cluster of differentiation 36; *TCF7L2*, transcription factor 7 like 2; *LCT*, lactase; *PPARG*, peroxisome proliferator activated receptor gamma; *PNPLA3*, patatin like phospholipase domain containing 3; *TAS1R2*, taste 1 receptor member 2; *VDR*, vitamin D receptor; *CYP1A2*, cytochrome P450 family 1 subfamily A member 2; *TXN*, thioredoxin; SFA, saturated fatty acids; MUFA, monounsaturated fatty acids; T2DM, type 2 diabetes mellitus; CVD, cardiovascular disease.

These scientific advances are contributing to the prevention and treatment of chronic diseases since they potentially allow to (1) predict individual risks, (2) explain their etiology, and (3) enable the personalization of their nutritional management [14, 15].

Indeed, SNPs (or more generally speaking, SNV, single nucleotide variants, a term that comprises both common and low-frequency alleles) are by far the most widely studied genetic variation in the field of precision nutrition. In this sense, several SNPs have been associated with common chronic diseases through interactions with the intakes of macro- and micronutrients, or with the consumption of particular foods and dietary patterns (Table 1). Examples include polymorphisms in genes related to taste perception including the sweet taste receptor (*TAS1R2*) [16] and cluster of differentiation 36 (*CD36*) [17], which were associated with dyslipidemia in Mexican subjects consuming high amounts of carbohydrates and fats, respectively. Common variants in genes regulating homocysteine metabolism, such as methylenetetrahydrofolate reductase (*MTHFR*), and methionine synthase (*MTR*), have been linked to increased risk for breast cancer in individuals with low intakes of folate, vitamin B_6, and vitamin B_{12} [18]. Also, it has been reported that in addition to

sunlight, vitamin D status can also be influenced by several polymorphisms in vitamin D pathway genes [19], thereby modulating its biological functions in the organism. Interestingly, SNPs in the vitamin D receptor (*VDR*) gene, which affect vitamin D availability [20, 21], have been associated with osteoporosis predisposition in postmenopausal women with low calcium intakes [22]. Moreover, SNPs in genes encoding lipid proteins such as apolipoprotein C3 (*APOC3*) and apolipoprotein A1 (*APOA1*) conferred a higher risk of metabolic syndrome in subjects with a Western dietary pattern [23, 24]. Likewise, a genetic variant in the cytochrome P450 family 1 subfamily A member 2 (*CYP1A2*) gene was associated with an increased risk of hypertension and CVD in moderate and heavy coffee drinkers [25, 26]. Additionally, studies using genetic risk scores (GRS) have examined the cumulative effect of SNPs on diet interactions and disease susceptibility. Thus, macronutrient intake was shown to modify the association of an obesity GRS with greater values of adiposity [27]. Significant interactions between saturated fat intake and obesity GRS were also found to modulate BMI in two American populations [28]. Furthermore, obesity GRS interacted with the intake of sugar-sweetened beverages [29], and fried food consumption [30] in relation to BMI and obesity in several cohort studies.

Nutrigenetics is defined as the science that studies the effect of genetic variation on dietary response [13]. Thus, SNPs-diet interactions have also been reported to be involved in the differential responses to nutritional interventions aimed at restricting total caloric intake or modifying energy derived from fat, protein, or carbohydrates (Table 2). In this sense, studies performed in a range of populations have investigated the effects of several SNPs on weight loss, weight regain and metabolic improvements concerning serum lipid levels and insulin resistance (Table 2). These investigations include polymorphisms in or near genes involved in the regulation of food intake, lipid and lipoprotein metabolism, insulin signaling, glucose homeostasis, inflammatory response, amino acid metabolism, and circadian cycle (Table 2). Regarding the effects of GRS on dietary responses, individuals with lower GRS for T2DM had greater improvements in insulin resistance and β-cell function when consuming a low-protein diet [31]. Conversely, subjects with higher GRS for glucose disorders had greater increases in fasting glucose when consuming a high-fat diet [32]. Moreover, a GRS built from genes identified by genome-wide association studies, partially explained the variation in triglyceride changes in response to omega-3 fatty acid supplementation [33].

Additionally, SNPs have been included in nutrigenetic tests with the aim of evaluating their impact on changing eating habits. For example, it was shown that gene-based personalized nutrition targeting the apolipoprotein E (*APOE*) gene was more effective in reducing saturated fat intake compared with standard dietary advice [34]. Also, greater Mediterranean diet scores were reported among participants who received gene-based personalized nutrition targeting specific variants in five nutrient-responsive genes compared with those who received dietary advice on the basis of current diet plus phenotype [35]. Furthermore, it was reported that disclosure of genetic information regarding angiotensin I converting enzyme (*ACE*) genotype for personalized nutrition resulted in greater changes in sodium intake compared to general population-based dietary advice [36]. Likewise, individuals who were informed about their fatty acid desaturase 1 (*FADS1*) genotype were more aware of the role of omega-3 fatty acids in health, and reported fewer barriers to their consumption, compared with those who did not receive their personal genetic information [37]. These findings are related to a better understanding, awareness, and usefulness of dietary recommendations based on genetics than general dietary advice [38].

In addition to SNPs, previous studies have found evidence of an association between CNVs and the risk of metabolic diseases. For example, CNV in the leptin receptor (*LEPR)* gene was found to be associated with metabolic traits and the risk of T2DM [39]. Moreover,

Table 2. Certain nutrigenetic trials analyzing SNPs-diet interactions involved in the differential responses to nutritional interventions

Genes	Polymorphisms	Alleles	Diet interactions	Dietary responses	Ref.
FTO	rs1558902	A	High protein	Greater weight loss	[118]
FTO	rs1558902	A	Low fat	Less reductions in insulin and HOMA-IR	[119]
TCF7L2	rs7903146	T	High fat	Smaller weight loss and HOMA-IR	[120]
APOA5	rs964184	G	Low fat	Greater reduction in TC and LDL-c	[121]
GIPR	rs2287019	T	Low fat	Greater weight loss and greater decreases in glucose, insulin and HOMA-IR	[122]
CETP	rs3764261	C	High fat	Larger increases in HDL-c and decreases in triglycerides	[123]
DHCR7	rs12785878	T	High protein	Greater decreases in insulin and HOMA-IR	[124]
LIPC	rs2070895	A	Low fat	Higher decreases in TC and LDL-c and a lower increase in HDL-c	[125]
PPM1K	rs1440581	C	High fat	Less weight loss and smaller decreases in insulin and HOMA-IR	[126]
TFAP2B	rs987237	G	High protein	Higher weight regains	[127]
IRS1	rs2943641	C	High carbohydrate	Greater decreases in insulin, HOMA-IR and weight loss	[128]
PCSK7	rs236918	G	High carbohydrate	Higher decreases in insulin and HOMA-IR	[129]
MTNR1B	rs10830963	G	High protein	Lower weight loss in women	[130]
IL6	rs2069827	C	Mediterranean diet	Lower weight gains	[131]

FTO, fat mass and obesity associated; *TCF7L2*, transcription factor 7 like 2; *APOA5*, apolipoprotein A5; *GIPR*, gastric inhibitory polypeptide receptor; *CETP*, cholesteryl ester transfer protein; *DHCR7*, 7-dehydrocholesterol reductase; *LIPC*, lipase C, hepatic type; *PPM1K*, protein phosphatase, Mg^{2+}/Mn^{2+} dependent 1K; *TFAP2B*, transcription factor AP-2 beta; *IRS1*, insulin receptor substrate 1; *PCSK7*, proprotein convertase subtilisin/kexin type 7; *MTNR1B*, melatonin receptor 1B; *IL6*, interleukin-6; TC, total cholesterol; LDL-c, low-density lipoprotein cholesterol; HDL-c, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance.

low copy number of the salivary amylase alpha 1A (*AMY1A*) gene has been related to a predisposition for obesity, suggesting a link between carbohydrate metabolism and obesity [40, 41]. Another DNA biomarker is the pentanucleotide (CTTTA) Del/Ins variant in the 3′-UTR of the *LEPR* gene, which has been associated with the risk of T2DM [42]. Further studies are needed to assess possible interactions between these genetic variants and dietary intake in relation to disease risk as well as their effects on dietary response, but such investigations provide examples of the direction in which future research in the field should be headed.

Diet and Gene Expression Profiles

Nutrition may exert an impact on health outcomes by directly affecting the expression of genes that regulate critical metabolic pathways [43]. In this sense, the science of nutrigenomics studies the role of nutrients and bioactive food compounds in gene expression and,

Table 3. Nutrigenomic examples of interactions between dietary intakes and gene expression profiles involved in disease risk

Dietary factors	Target genes	Expression changes	Putative disease risks	Ref.
Low protein	*NR1H3*	–	T2DM	[47]
Low protein	*HSD11B1*, *PCK1*	+	T2DM	[47]
Choline and folate deficiency	*PPARGA*	–	NAFLD	[48]
Chromium deficiency	Insulin signaling genes	–	T2DM	[49]
Selenium deficiency	*TLR2*, *ICAM1*	+	CVD	[50]
Vitamin B_{12} deficiency	*SREBF1*, *LDLR*	+	Dyslipidemia	[51]
Vitamin A deficiency	*GATA4*	–	CVD	[52]
High fat and high sugar	*LEP*, *SREBF1*, *PLIN*	+	Obesity	[65]
High fat	*OPRM1*, *PENK*, *DAT*	+	Obesity	[74]
Low protein	*CYP7A1*	–	Dyslipidemia	[75]
Selenium deficiency	*VHL*	–	Cancer	[79]
Vitamin D deficiency	*NFKBIA*	–	T2DM	[80]
High SFA	*TNFA*, *IL6*	+	CVD	[132]
High SFA	Proinflammatory "obesity-linked" genes	+	Obesity-related inflammation	[133]
High SFA	*PPARGC1A*	–	NAFLD	[134]
High SFA	*ADGRE1*	+	Obesity-related inflammation	[134]
High fat	*LEPR*, *NPY*	+	Obesity	[135]
High fat	*TH*, *DRD4*	+	Obesity	[136]
High fat rich in lard	*OPN*, *ADGRE1*, *TNFA*, *NFKB1*	+	Obesity-related inflammation and insulin resistance	[137]
High fat rich in lard	*OPN*, *TLR2*, *TLR4*, *TNFA*	+	Obesity-related inflammation and insulin resistance	[138]
High fat and high sugar	*DRD2*	–	Obesity	[139]
High fat and high sugar	*NPY*	+	Obesity	[140]
High fat and high sugar	*POMC*	–	Obesity	[140]
High carbohydrate	*FGF21*	+	NAFLD	[141]
Low folate and choline	Genes involved in cellular proliferation	+	Liver cancer	[142]
Western diet plus vitamin D deficiency	*TLR2*, *TLR4*, *TLR9*, *IL1B*, *IL4*, *IL6*, *RETN*	+	NAFLD	[143]
Choline and folate deficiency	*APOE*, *FOXA1*, *FOXA2*	–	NAFLD	[144]

SFA, saturated fatty acids; *TNFA*, tumor necrosis factor alpha; *IL6*, interleukin-6; *PPARGC1A*, peroxisome proliferative activated receptor, gamma, coactivator 1 alpha; *ADGRE1*, adhesion G protein-coupled receptor E1; *LEPR*, leptin receptor; *NPY*, neuropeptide Y; *TH*, tyrosine hydroxylase; *DRD4*, dopamine receptor D4; *OPRM1*, opioid receptor, mu 1; *PENK*, preproenkephalin; *DAT*, dopamine transporter; *OPN*, osteopontin; *NFKB1*, nuclear factor kappa B subunit 1; *TLR2*, toll-like receptor 2; *TLR4*, toll-like receptor 4; *DRD2*, dopamine receptor D2; *POMC*, proopiomelanocortin; *LEP*, leptin; *SREBF1*, sterol regulatory element binding transcription factor 1; *PLIN*, perilipin; *FGF21*, fibroblast growth factor 21; *CYP7A1*, cytochrome P450 family 7 subfamily A member 1; *NR1H3*, nuclear receptor subfamily 1 group H member 3; *HSD11B1*, hydroxysteroid 11-beta dehydrogenase 1; *PCK1*, phosphoenolpyruvate carboxykinase 1; *TLR9*, toll-like receptor 9; *IL1B*, interleukin-1 beta; *IL4*, interleukin-4; *RETN*, resistin; *APOE*, apolipoprotein E; *FOXA1*, forkhead box A1; *FOXA2*, forkhead box A2; *PPARA*, peroxisome proliferator activated receptor alpha; *LDLR*, low-density lipoprotein receptor; *NFKBIA*, NFKB inhibitor alpha; *GATA4*, GATA binding protein 4; *ICAM1*, intercellular adhesion molecule 1; VHL, von Hippel-Lindau; CVD, cardiovascular disease; T2DM, type 2 diabetes mellitus; NAFLD, nonalcoholic fatty liver disease.

consequently, on the proteome and the metabolome [44]. To date, a large number of studies have evaluated the effect of different dietary factors on gene expression profiles, which are related to disease susceptibilities (Table 3). With regard to dietary patterns, subjects following a Western dietary pattern, characterized by high intakes of refined grain products, desserts, sweets, and processed meats, showed a gene expression profile associated with inflammatory response and cancer signaling compared to those who consumed high amounts of vegetables, fruits, and whole grain products [45]. Similarly, pathway analyses revealed that high meat

consumption was associated with gene networks linked to cancer in colon tissue [46]. High-fat diets, especially rich in saturated fatty acids, have induced gene expression profiles related to inflammation, glucose intolerance, and liver lipid accumulation, as well as upregulation of neuropeptide expression involved in obesity development (Table 3). On the other hand, low-protein diets enhanced hepatic gluconeogenic gene expression with subsequent glucose intolerance [47]. Also, choline- and folate-deficient diets were associated with dysregulation of genes involved in lipid metabolism, thus influencing the susceptibility and severity of NAFLD [48]. Chromium deficiency downregulated insulin signaling genes, thus demonstrating a role in T2DM pathogenesis [49], whereas deprivations of selenium [50], vitamin B_{12} [51], and vitamin A [52], could increase CVD susceptibility by upregulating proinflammatory and lipogenic genes.

Experimental studies have shown the beneficial effects of nutrients and bioactive food compounds as a result of the regulation of critical gene expressions (Table 4). In this sense, it has been reported that consuming a Mediterranean diet reduces the postprandial expression of genes that encode proteins related to inflammation, endoplasmic reticulum stress, atherogenesis, and oxidative stress [53–55]. Also, high intakes of monounsaturated fatty acids through the consumption of olive oil have been associated with a low expression of genes involved in inflammation and abnormal lipid storage [55, 56]. Diets with a high content of polyunsaturated fatty acids favorably regulate the expression of neuropeptide genes involved in energy homeostasis [57]. Moreover, energy-restricted diets supplemented with eicosapentaenoic acid, and α-lipoic acid have been associated with upregulation of fatty acid-oxidizing genes, as well as downregulation of lipogenic and proinflammatory genes [58, 59]. In contrast, high-protein diets prevent and reverse NAFLD by modulating the expression of genes involved in liver lipid metabolism [60, 61]. Concerning the effects of bioactive food compounds on gene expression, those most widely studied include green tea, theaflavin (black tea), sulforaphane (cruciferous vegetables), resveratrol (grapes and red wine), curcumin (turmeric), genistein (soy bean), and several apple polyphenols (Table 4). Thus, epigallocatechin-3-gallate, theaflavin, curcumin, sulforaphane, and genistein may exert anticancer properties by upregulating tumor suppressor genes and conversely, downregulating tumor promoting genes (Table 4). In addition, curcumin and resveratrol have shown antiatherogenic effects by decreasing the expression of matrix metalloproteinases, which are involved in plaque formation and progression [62–64]. Of note, apple polyphenols apparently prevented diet-induced obesity through the regulation of genes involved in adipogenesis, lipolysis, and fatty acid oxidation [65].

Interestingly, gene expression profiles have also been used to predict the responsiveness to nutritional treatments. In this area, it has been reported that, prior to the consumption of a low-fat diet, adipose gene expression profiling was able to differentiate responders from nonresponders, as well as serve as a weak predictor of subjects predisposed to lose weight [66]. Also, the analysis of gene expression in subcutaneous adipose tissue revealed that genes regulating fatty acid metabolism, citric acid cycle, oxidative phosphorylation, and apoptosis were differentially regulated during a low-calorie diet between weight maintainers and weight regainers after weight loss [67]. Moreover, expression levels of proinflammatory genes were higher at the end of a low-calorie diet in subjects who after dietary-induced weight loss subsequently regained weight [68]. Differentially expressed genes in adipose tissue were also observed between successful and unsuccessful subjects after an energy restriction-induced weight loss program [69]. In this study, pathway analyses revealed that the main biological processes represented in adipose tissue from subjects who regained weight included cellular growth and proliferation, cell death, cellular function, and maintenance, whereas mitochondrial oxidative phosphorylation was the major network associated with continued weight loss [69].

Table 4. Certain nutrigenomic studies assessing gene expression profiles associated with nutritional interventions

Nutritional interventions	Target genes	Expression changes	Potential health effects	Ref.
Mediterranean diet	*NFKB1*, *IKBKB*, *MMP9*, *IL1B*, *MAPK8*, *XBP1*	–	Anti-inflammatory, antiatherogenic	[53]
Mediterranean diet plus olive oil	*NFKB1*, *MMP9*, *TNFA*	–	Anti-inflammatory, antiatherogenic	[55]
Mediterranean diet	*NFE2L2*, *SOD1*, *SOD2*, *TXNRD1*	–	Anti-inflammatory, antioxidant	[54]
High MUFA	*APOBR*	–	Antilipidemic, antiatherogenic	[56]
Energy-restricted diet plus EPA	*IL10*	+	Anti-inflammatory	[58]
High PUFA	*POMC*, *GALP*	+	Antiobesity	[57]
High PUFA	*HCRT*, *MCH*	–	Antiobesity	[57]
Energy-restricted diet plus EPA and α-lipoic acid	Lipid catabolism genes	+	Antilipidemic	[59]
Energy-restricted diet plus EPA and α-lipoic acid	Lipid storage genes	–	Anti-lipidemic	[59]
High protein	*PPARGC1A*, *PCK1*, *GSTA*, *CPT1A*	+	Antisteatotic	[60, 61]
High protein	*FGF21*, *SCD1*	–	Antisteatotic	[60, 61]
Curcumin	*MMP-9*, *MMP-13*, *EMMPRIN*	–	Antiatherogenic, anticancer	[62, 63]
Resveratrol	*EMMPRIN*	–	Antiatherogenic	[64]
Apple polyphenols	*LEP*, *SREBF1*, *PLIN*	–	Antiobesity	[65]
Apple polyphenols	*PPARGC1A*, *AQP7*, *AEBP1*	+	Antiobesity	[65]
Flavonoid-fish oil supplement	Phagocytosis-related inflammatory genes	–	Anti-inflammatory	[145]
High n-3/n-6 PUFA ratio	*TLR4*, *TNFA*, *IL6*, *CRP*	–	Anti-inflammatory, antidiabetic	[146]
EGCG	*MMP9*, *MMP2*	–	Antitumorigenic	[147, 148]
Theaflavin	*MMP2*	–	Antitumorigenic	[149]
Resveratrol	*FASN*	–	Antisteatotic	[150]
Sulforaphane	*EGR1*	+	Anticancer	[151]
Genistein	*P21*, *P16*	+	Anticancer	[152]
Genistein	*BMI1*, *c-MYC*	–	Anticancer	[152]

MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids; *NFKB1*, nuclear factor kappa B subunit 1; *IKBKB*, inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase beta; *MMP9*, matrix metallopeptidase 9; *IL1B*, interleukin 1 beta; *MAPK8* (*JNK1*), mitogen-activated protein kinase 8; *XBP1*, X-box binding protein 1; *TNFA*, tumor necrosis factor alpha; *APOBR*, apolipoprotein B receptor; *NFE2L2*, nuclear factor, erythroid 2 like 2; *SOD1*, superoxide dismutase 1; *SOD2*, superoxide dismutase 2; *TXNRD1*, thioredoxin reductase 1; *IL10*, interleukin 10; *POMC*, proopiomelanocortin; *GALP*, galanin like peptide; *HCRT*, hypocretin neuropeptide precursor; *MCH*, melanin-concentrating hormone; *PPARGC1A*, peroxisome proliferative activated receptor, gamma, coactivator 1 alpha; *PCK1*, phosphoenolpyruvate carboxykinase 1; *GSTA*, glutathione S-transferase cluster; *CPT1A*, carnitine palmitoyltransferase 1A; *FGF21*, fibroblast growth factor 21; *SCD1*, stearoyl-coenzyme A desaturase 1; *TLR4*, toll-like receptor 4; *IL6*, interleukin 6; *CRP*, C-reactive protein; *MMP2*, matrix metallopeptidase 2; *MMP13*, matrix metallopeptidase 13; *EMMPRIN*, extracellular matrix metalloproteinase inducer; *FASN*, fatty acid synthase; *EGR1*, early growth response 1; *LEP*, leptin; *SREBF1*, sterol regulatory element binding transcription factor 1; *PLIN*, perilipin; *AQP7*, aquaporin 7; *AEBP1*, adipocyte enhancer binding protein 1.

Diet and Epigenetic Signatures

Epigenetics has been defined as "inheritable and reversible processes that regulate gene expression without concomitant changes in the DNA coding sequence" [70]. The epigenetic control of gene expression is involved in critical biological and physiological processes, such as imprinting, silencing of specific chromosomal domains, embryonic development, cellular differentiation, and organogenesis [71]. However, dysregulation of epigenetic phenomena

Table 5. Nutriepigenetic examples of interactions between dietary intakes and epigenetic modifications involved in disease risk

Dietary factors	Epigenetic signatures	Modification types	Putative disease risks	Ref.
Low protein	*NR1H3* acetylation	–	T2DM	[47]
Chromium deficiency	Methylation of insulin signaling genes	+	T2DM	[49]
Selenium deficiency	*TLR2*, *ICAM1* methylation	–	CVD	[50]
Vitamin B_{12} deficiency	*SREBF1*, *LDLR* methylation	–	Dyslipidemia	[51]
Vitamin A deficiency	*GATA4* methylation	+	CVD	[52]
High fat and high sugar	*LEP* methylation	+	Obesity	[65]
High fat	*OPRM1*, *PENK*, and *DAT* methylation	–	Obesity	[74]
Low protein	*CYP7A1* acetylation	–	Dyslipidemia	[75]
Choline and folate deficiencies	miR-134, miR-409-3p, miR-410 and miR-495 expressions	+	NAFLD	[76]
Choline and folate deficiencies	miR-34a, miR-122, miR-181a, miR-192, and miR-200b expressions	+	NAFLD	[77]
Low folate, vitamin A, vitamin B_1, potassium, iron	*P16*, *P14*, and *hMLH1* methylation	+	Cancer	[78]
Selenium deficiency	*VHL* methylation	+	Cancer	[79]
Vitamin D deficiency	*NFKBIA* methylation	+	T2DM	[80]
Calcium deficiency	*HSD11B1* methylation	–	T2DM	[81]
Magnesium deficiency	*HSD11B2* methylation	+	T2DM	[82]
High fat and high sugar	*FASN* methylation	–	Obesity, NAFLD	[88]
Choline and folate deficiencies	*APOE*, *FOXA1*, and *FOXA2* methylation	+	NAFLD	[144]
High fat and high sugar	*FASN* methylation	–	Obesity, NAFLD	[153]
Low fruit consumption and folate deficiency	*LINE-1* methylation	–	Cancer	[154]

LEP, leptin; *FASN*, fatty acid synthase; *OPRM1*, opioid receptor, mu 1; *PENK*, preproenkephalin; *DAT*, dopamine transporter; *CYP7A1*, cytochrome P450 family 7 subfamily A member 1; *NR1H3*, nuclear receptor subfamily 1 group H member 3; *LINE-1*, long interspersed element-1; *MLH1 (HMLH1)*, mutL homolog 1; *APOE*, apolipoprotein E; *FOXA1*, forkhead box A1; *FOXA2*, forkhead box A2; *SREBF1*, sterol regulatory element binding transcription factor 1; *LDLR*, low-density lipoprotein receptor; *NFKBIA*, NFKB inhibitor alpha; *GATA4*, GATA binding protein 4; *TLR2*, toll-like receptor 2; *ICAM1*, intercellular adhesion molecule 1; *VHL*, von Hippel-Lindau; *HSD11B1*, hydroxysteroid 11-beta dehydrogenase 1; *HSD11B2*, hydroxysteroid 11-beta dehydrogenase 2; CVD, cardiovascular disease; T2DM, type 2 diabetes mellitus; NAFLD, nonalcoholic fatty liver disease.

can alter phenotype and cell function, leading to the onset and progression of diverse chronic diseases [72, 73]. In this sense, complex interactions among nutritional factors and DNA methylation, covalent histone modifications and noncoding RNAs, including microRNAs (miRNAs), have been implicated in obesity, dyslipidemia, T2DM, NAFLD, cancer, and CVD (Table 5). For example, high-fat and sugar diets have been related to abnormal methylation patterns of neuropeptide genes controlling food intake, which may contribute to the development of obesity [65, 74]. Low-protein diets induced glucose [47] and lipid alterations by disrupting histone modifications in key regulatory genes [75]. Also, choline and folate shortages enhanced miRNAs changes responsible for the progression of NAFLD [76, 77]. Different micronutrient deficiencies such as folate, vitamin A, vitamin B, potassium, iron, and selenium correlated with hypermethylation of tumor suppressor genes, demonstrating a role in cancer [78, 79]. Deprivations of vitamin D [80], calcium [81], magnesium [82], and chromium [49] could increase the risk of developing T2DM through promoting aberrant methylation patterns in genes involved in glucose homeostasis, insulin signaling and inflammatory response. Additionally, deficits of selenium [50] and vitamin A were associated with the pathogenesis of CVD by affecting the DNA methylation status of critical genes [52].

Table 6. Certain nutriepigenetic studies evaluating epigenetic modifications related to diverse nutritional interventions

Nutritional interventions	Epigenetic signatures	Modification types	Potential health effects	Ref.
Apple polyphenols	*SREBF1* methylation	–	Antiobesity	[65]
Apple polyphenols	*PPARGC1A* methylation	+	Antiobesity	[65]
Mediterranean diet	*EEF2*, *IL4I1* methylation	–	Anti-inflammatory	[84]
Mediterranean diet	*MAPKAPK2* methylation	+	Anti-inflammatory	[84]
Mediterranean diet	*IL6* methylation	+	Anti-inflammatory	[85]
Fish oil and pectin	miR-19b, miR-26b, miR-203 expressions	+	Anticancer	[86]
DHA	miR-192, miR-30c expressions	+	Antilipidemic	[87]
Pterostilbene	*FASN* methylation	+	Antiobesity	[88]
Curcumin	p300 HAT activity	–	CVD prevention	[89]
Curcumin	*FGFR3*, *FZD10*, *GPX4*, *HOXD3* methylation	–	Antifibrotic	[90]
Resveratrol	miR-129, miR-328-5p, miR-539-5p		Antilipidemic	[149]
Genistein	P21, P16 chromatin activators	+	Anticancer	[151]
Genistein	P21, P16 chromatin repressors	–	Anticancer	[151]
Methyl donor supplementation	*FASN* methylation	+	Antisteatotic	[155]
Extra-virgin olive oil	CNR1 (CB1) methylation	–	Anticancer	[156]
PUFA	Global DNA methylation	+	Anticancer	[157]
Resveratrol	*BRCA-1* methylation	–	Anticancer	[158]
Resveratrol	miR-101b, miR-455 expressions	+	Anti-inflammatory, anticancer	[159]
Resveratrol	Sirt1 activation	+	Anti-inflammatory, anticancer	[160, 161]
EGCG	*RXRA* methylation	–	Anticancer	[162]
EGCG	miR-16 expression	+	Anticancer	[163]
Green tea polyphenols and EGCG	EZH2, class I HDAC activity	–	Anticancer	[164]
Green tea polyphenols and EGCG	P53 acetylation	+	Anticancer	[165]
Curcumin	miR-22 expression	+	Anticancer	[166]
Sulforaphane	HDAC activity	–	Anticancer	[167, 168]
Sulforaphane	P21 acetylation	+	Anticancer	[168]
Genistein	P21, P16 acetylation	+	Anticancer	[169]

DHA, docosahexaenoic acid; PUFA, polyunsaturated fatty acid; EGCG, epigallocatechin-3-gallate; *EEF2*, eukaryotic translation elongation factor 2; *IL4I1*, interleukin-4 induced 1; *MAPKAPK2*, mitogen-activated protein kinase-activated protein kinase 2; *IL6*, interleukin-6; CNR1 (CB1), cannabinoid receptor 1; *BRCA1*, DNA repair associated; sirt1, sirtuin 1; *FASN*, fatty acid synthase; *RXRA*, retinoid X receptor alpha; EZH2, enhancer of zeste homolog 2; *FGFR3*, fibroblast growth factor receptor 3; *FZD10*, frizzled class receptor 10; *GPX4*, glutathione peroxidase 4; *HOXD3*, homeobox D3; HATs, acetyltransferases; HDACs, histone deacetylases; H3, histone 3; *ERS1*, estrogen receptor 1 (alpha); *SREBF1*, sterol regulatory element binding transcription factor 1; *PPARGC1A*, peroxisome proliferative activated receptor, gamma, coactivator 1 alpha.

On the other hand, the reversible feature of epigenetic marks has given rise to the design of specific nutritional interventions aimed at reversing epigenetic alterations that might have a significant impact on preventing and treating human chronic diseases (nutriepigenetics) [83]. Thus, several experimental studies have investigated the epigenetic mechanisms underlying the health effects of certain nutrients and bioactive food components (Table 6). For instance, it was found that the anti-inflammatory effects of consuming a Mediterranean diet

were related to hypermethylation of proinflammatory genes [84, 85]. The administrations of polyunsaturated fatty acids positively modulated the expression of several miRNAs, which suppressed oncogenic and lipogenic genes [86, 87]. Also, the anticancer properties of resveratrol, epigallocatechin-3-gallate, curcumin, sulforaphane, and genistein have been associated with some epigenetic modifications including hypomethylation and acetylation of tumor suppressor genes, and an increase in miRNAs targeting oncogenes (Table 6). Likewise, apple polyphenols and pterostilbene (a derivate of resveratrol), prevented diet-induced obesity by regulating the methylation status of genes involved in lipid metabolism [65, 88]. Furthermore, it was reported that curcumin exerted protective effects against liver injury and heart failure through modulating DNA methylation patterns and histone modifications of key genes [89, 90]. Based on this evidence, it has been proposed that the introduction of these dietary compounds into an "epigenetic diet" could serve as an effective strategy for reducing the incidence of obesity and associated comorbidities [91]. Additionally, studies have shown that some of the health benefits of energy restriction are mediated partially by epigenetic mechanisms including prevention of aberrant DNA methylation patterns and chromatin alterations [92]. Thus, it has been reported that moderate energy reductions might contribute to delay the onset of some aging-related diseases and extend lifespan through epigenetic mechanisms [93].

Of note, epigenetic marks have also been found to modulate the effect of nutritional treatments on weight loss and changes in metabolic profiles, which could be used as biomarkers to predict the responsiveness to dietary prescriptions [94]. For example, methylation levels of circadian genes correlated with the magnitude of weight loss and circulating blood lipids after a nutritional program based on a Mediterranean dietary pattern [95, 96]. Similarly, methylation patterns of appetite-regulatory genes were associated with the success in weight loss or the risk of weight regain [97, 98]. Moreover, reductions of body fat and serum lipids were related to changes in the methylation status of genes involved in inflammatory response and fatty acid metabolism [99, 100]. Furthermore, differential baseline expression of several miRNAs was found between responders and nonresponders to a weight-loss trial that consisted of following an energy-restricted treatment [101].

As a final point, it is important to highlight that there may be interactions between the different genetic/epigenetic approaches, which may modulate the effectiveness of precision nutrition on the treatment of some chronic diseases. For example, in vitro studies demonstrated that the effects of omega-3 fatty acids supplementation on plasma triglyceride clearance through increasing transcription rates of lipoprotein lipase *(LPL)* gene, were dependent on the L162V polymorphism in the peroxisome proliferator-activated receptor alpha (*PPARA*) gene [102]. Another study reported that gene expression levels of *PPARA* and apolipoprotein A1 (*APOA1*) were influenced by the *PPARA* L162V polymorphism after the supplementation of omega-3 fatty acids [103]. Furthermore, it was found that changes in plasma triglycerides in response to omega-3 fatty acid supplementation could be modulated by the effect of polymorphisms and DNA methylation on expression levels of key genes identified by genome-wide association studies [104]. Additionally, genetic variants in genes encoding the selenoproteins glutathione peroxidase (*GPX1*) and selenoprotein P (*SEPP*) could influence their gene expressions in response to supplementation with a selenium-rich Brazil nut, suggesting a possible role in the nutritional treatment of chronic degenerative conditions [105].

Concluding Remarks

The adverse impacts of metabolic diseases including obesity and associated chronic comorbidities on public health remain a major concern due to the lack of effective interventions for their prevention and management. The absence of relevant progress despite

persistent efforts may be partially explained by the fact that current strategies are based on nutritional recommendations for general populations, and do not consider the influence of genetic/epigenetic factors and their interaction with the environment (mainly diet and physical activity). Precision nutrition is an important part of personalized medicine and an emerging approach for disease prevention and treatment that takes into account genetic/epigenetic information, as well as age, gender, physiopathological status and environmental issues, including personal lifestyle. In recent years, genomic sciences have been contributing to a better understanding of how genetic variants and epigenetic modifications are involved in the development of diverse pathological conditions and the way in which they may modify responses to therapy. This knowledge has led to the search for genetic and epigenetic biomarkers to predict the risk of developing chronic diseases. Another potential therapeutic target is the use of nutritional interventions based on certain nutrients and bioactive dietary compounds that can modify epigenetic marks and gene expression. Although caution must be exercised, these scientific insights are paving the way for the design of innovative strategies for the prevention, management, and treatment of obesity and other prevalent chronic diseases with a genetic background within the era of precision nutrition.

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