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Review Article

Variations in Adipokine Genes *AdipoQ*, *Lep*, and *LepR* Are Associated with Risk for Obesity-Related Metabolic Disease: The Modulatory Role of Gene-Nutrient Interactions

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Obesity rates are rapidly increasing worldwide and facilitate the development of many related disease states, such as cardiovascular disease, the metabolic syndrome, type 2 diabetes mellitus, and various types of cancer. Variation in metabolically important genes can have a great impact on a population's susceptibility to becoming obese and/or developing related complications. The adipokines adiponectin and leptin, as well as the leptin receptor, are major players in the regulation of body energy homeostasis and fat storage. This paper summarizes the findings of single nucleotide polymorphisms in these three genes and their effect on obesity and metabolic disease risk. Additionally, studies of gene-nutrient interactions involving adiponectin, leptin, and the leptin receptor are highlighted to emphasize the critical role of diet in susceptible populations.

1. Introduction

Obesity is the result of an imbalance in energy homeostasis and is characterized by increased adipose tissue mass, chronic low-grade inflammation, insulin resistance, and endothelial dysfunction. Obesity is a major risk factor for type 2 diabetes mellitus (T2DM), cardiovascular disease (CVD), and several types of cancer [1–3], and lies at the core of a cluster of metabolic abnormalities defined as the metabolic syndrome, which includes insulin resistance and hyperinsulinemia, hypertension, impaired glucose tolerance, and T2DM [4]. According to the National Health and Nutrition Examination Survey (NHANES), 33.8% of American adults are obese (BMI $\geq$ 30) and 68.0% are considered overweight or obese (BMI $\geq$ 25) [5]. Dietary choices (and overeating) in combination with low physical activity are typically attributed as the root cause of the rapid spread of the obesity epidemic in the modern world [6], but genetic factors are a strong determinant of individual susceptibility to obesity. The growing prevalence of obesity and obesity-related pathologies has spurred the search for greater insight into the mechanisms that contribute to the development of obesity and its complications.

Adipose tissue plays multiple important roles in body weight regulation and energy homeostasis. Adipose functions as an energy storage organ, storing fat primarily in the form of triglycerides and releasing free fatty acids as the body's energy demands change. Adipose tissue is also an active endocrine organ, secreting many cytokines, chemokines, and hormone-like factors. These molecules, which are produced and secreted primarily by adipocytes, are known as adipokines [7]. Adipokines constitute a diverse group of bioactive peptides with many and varied roles, including mediation of glucose and lipid metabolism, blood pressure regulation, and modulation of inflammation and immune function [8]. While over 100 adipokines have been identified [9], the specific functions of many of

these molecules are poorly understood. Regardless, it has been clearly established that in obesity, adipocytes undergo hypertrophy and become dysfunctional [10, 11]. As a result, the adipokine profile they express and secrete is altered, leading to a proinflammatory environment both locally and systemically, and contributing to the pathological effects of obesity.

Since many critical metabolic functions are influenced by adipokines, genetic variations that affect their efficacy may contribute to various pathophysiological states. For instance, genetic variation in adipokine genes has been shown to modulate circulating adipokine levels and thus could predispose carriers of single nucleotide polymorphisms (SNPs) to developing obesity or other metabolic illnesses in which adipokines play a prominent role, or alternatively, provide them some protection against disease. Studying the impact of such gene polymorphisms in human populations can provide insight into the roles specific adipokines play in obesity and related pathologies. This paper will discuss the association of SNPs in the protein-coding genes for two well-studied adipokines, adiponectin and leptin, as well as the leptin receptor, in the context of obesity-related metabolic disease. In addition, due to the profound effect that diet can have on weight gain and regulation, the recent literature on nutrient-gene interaction studies involving adipokines and dietary factors will be highlighted.

2. Methods

Articles for this review were identified using the PubMed/Medline databases. Search terms included "single gene polymorphism", "gene variant", "adiponectin", "AdipoQ", "leptin", "leptin receptor", and "obesity" or "metabolic disease". An emphasis was placed on studies published in the last decade, but the search was not limited to a specific time interval. The articles were chosen by scanning the abstract to ensure relevancy. Only studies in human populations and in English were included.

3. Adiponectin

Adiponectin is an important anti-inflammatory and insulin-sensitizing hormone and promotes lipid oxidation in tissues such as skeletal muscle and liver [12, 13]. Adiponectin also has direct antiatherosclerotic properties, as it strongly inhibits expression of adhesion molecules and growth factors [14]. Adiponectin serum levels are inversely correlated with body fat percentage in obese subjects, as well as in those afflicted with T2DM or coronary heart disease [15, 16]. Due to the protective nature of adiponectin in many types of cardiovascular and metabolic disease states, low serum levels of this adipokine are thought to contribute to the pathogenesis of these conditions. Several excellent reviews on the various roles of adiponectin are available [17–20]. The adiponectin gene *AdipoQ* has been identified as a susceptibility locus for the metabolic syndrome, T2DM and CVD [21, 22]. *AdipoQ* is located on chromosome 3q27. The gene is 15.8 kb long and contains three exons.

3.1. Adiponectin Levels and Obesity-Related Metabolic Disease Parameters. It is estimated that a 30–70% variation in normal circulating adiponectin levels can be attributed to genetic factors [23–29]. A total of 42 SNPs in *AdipoQ* and its regulatory region with a minor allele frequency of >1.5% have been identified [30]. Table 1 lists *AdipoQ* SNPs studied in the last decade and their relation (if any) to adiponectin levels and other obesity-related metabolic disease parameters. Since changes in adiponectin due to genetic variation are of particular interest in this paper, the table highlights the percent change in adiponectin levels in those studies that reported this parameter. Four SNPs (−11391 G > A, −11377 C > G, +45 T > G and +276 G > T) were analyzed with far greater frequency than any others and will be the focus of the following discussion.

The majority of studies analyzing the SNP −11391 G > A found a favourable increase in circulating adiponectin levels in those subjects carrying the A allele. A recent meta-analysis determined that SNP −11391 G>A was associated with adiponectin levels according to a dominant model with A allele carriers (GA and AA genotypes) having higher adiponectin levels compared with GG carriers [29]. An *in vitro* study supports these data, reporting a biological function of this SNP with the A allele enhancing *AdipoQ* promoter activity [31]. Despite the prevalence of the high adiponectin finding, most studies did not report any association with improved health in their subjects. Only one study, an analysis of a Caucasian population from Italy, showed a decrease in obesity-related risk factors (BMI, weight, and waist and hip circumference) [32]. Three studies had conflicting findings. In a study of European children carrying the A allele, adiponectin levels were found to be higher, similar to the situation in adults; however, the SNP showed an obesity-mediated detrimental association with fasting serum insulin and HOMA-IR [33]. A second study involving obese and morbidly obese French Caucasians found the SNP to be associated with lower adiponectin levels, but similarly accompanied by lower insulin sensitivity and a higher risk of T2DM [32]. In a third study, there was also an association between the GA genotype and risk of hyperglycemia in a population of French Caucasians [34]. While it is clear that most carriers of the A allele have raised adiponectin levels and could expect to be protected from metabolic disease, in certain populations the increase in adiponectin observed in GA and AA carriers appears to be too small to impart any appreciable metabolic advantage, where it fails to counterbalance the metabolic damages of obesity. In fact, it may contribute to the increased risk for childhood obesity and related insulin resistance.

The findings on the −11377 G > C SNP are inconsistent, but the general trend links the G allele to various detrimental conditions, including lower adiponectin levels [23, 42, 43, 45, 48], risk for developing hypertension [43], and, in some cases, risk for developing colorectal cancer [46]. On the other hand, the presence of the C allele has also been associated with higher BMI and obesity risk [31, 36], increased fasting glucose levels and T2DM risk [35, 42]. For example, a study that investigated genetic variations in adiponectin in individuals with metabolic syndrome found that SNP

Table 1: SNPs in the adiponectin gene *AdipoQ*.

SNP ID	Position	Parameter association	Population	Adiponectin level (% change)	*P* value	Reference
rs860291	−12823	No association with T2DM, BMI, or insulin sensitivity	Pima Indians			[24]
rs16861194	−11426 G > A	SNP associated with increased risk for gaining weight in diabetics	Chinese (T2DM)			[35]
		SNP associated with fasting plasma glucose in T2DM patients and in those with impaired glucose tolerance	Swedish Caucasians (T2DM/ impaired glucose tolerance/ nondiabetic)			[36]
		G allele moderately associated with T2DM	French Caucasians			[37]
rs17300539	−1391 G > A	A allele associated with higher adn levels, higher BMI, and obesity	Children of European origin	13.39	6.00*E*-08	[33]
		A allele carriers have lower weight, waist and hip circumferences and BMI				[32]
		GA carriers had increased risk for becoming hyperglycaemic/diabetic	French Caucasians			[34]
		A allele associated with higher adn levels	French Caucasians		.0001	[23]
		A allele associated with higher adn levels	Hispanic Americans and African Americans	18.89	.0001	[27]
		A allele associated with higher adn levels	Caucasians			[38]
		A allele associated with higher adn levels	Caucasian women	36.93	.0006	[39]
		A allele associated with higher adn levels in obese children	French Caucasians (obese/lean)		.005	[31]
		A allele associated with higher adn	Caucasian and African American adolescents	29.41	.002	[40]
		A allele associated with higher adn levels	Caucasians	19.05	.0005	[41]
		A associated with lower adn levels, lower insulin sensitivity, and higher risk of T2DM in obese subjects	French Caucasians (lean/obese)	32.01	.0003	[42]
rs266729	−11377 G > C	C allele associated with higher fasting plasma glucose levels in diabetics	Chinese (T2DM)			[35]
		C allele associated with severe obesity	French Caucasians (obese/lean)			[31]
		G allele associated with lower adn levels, higher risk of hypertension	Chinese (hypertensive)		.0037	[43]
		SNP associated with increase in plasma oxidative stress markers	T2DM patients			[44]

Table 1: Continued.

SNP ID	Position	Parameter association	Population	Adiponectin level (% change)	*P* value	Reference
		G allele associated with lower adn levels, lower insulin sensitivity, and higher risk of T2DM in obese subjects	French Caucasians (lean/obese)	20.66	.008	[42]
		G allele associated with coronary stenoses and lower adn levels	European men with CVD	26.92	.003	[45]
		SNP associated with increased risk for colorectal cancer	Czech patients			[46]
		No association with adn levels	Caucasian Italians			[32]
		No association with colorectal cancer risk	UK			[47]
		GG and CG associated with lower CRC risk	American CRC patients			[48]
		G associated with lower adn levels	French Caucasians		.0003	[23]
		CC and CG genotypes had higher BMI than GG	Swedish Caucasians (T2DM/ impaired glucose tolerance/ nondiabetic)			[36]
	−11365	SNP associated with lower plasma adn levels		18.36	.007	[49]
		No association with T2DM, BMI, or insulin sensitivity	Pima Indians			[24]
	−10677 C > T	SNP associated with lower adn levels	Chinese (hypertensive)		.0027	[43]
rs182052	−10068 G > A	A allele associated with lower adn levels	Hypertensive Chinese		.0001	[43]
		A allele associated with waist circumference	American Caucasian young adults			[50]
		G allele associated with higher adn	Caucasian and African American adolescents	17.58	0.03	[40]
	−10066 G > A	G allele associated with higher adn	Caucasian women	8.67	.01	[39]
rs16861209	−7734 C > A	A allele associated with higher adn	Caucasian women	22.68	.004	[39]
rs822395	−4041 A > C	No association with adn levels	Caucasian Italians			[32]
	−4034	CC associated with CVD risk				[49]
	−3971 G > A	A allele associated with worse glucose tolerance and insulin sensitivity, but not adn levels	Caucasian Canadians (nondiabetic)			[51]
rs2241766	+45 T > G	GG and TG genotypes were at higher risk for T2DM	Obese Iranians			[52]
		Both TG and GG genotypes were associated with gestational T2DM, whereas among healthy participants, the TT genotype had higher adn levels than other groups	Pregnant (<18 weeks) Malaysian women	19.92	.05	[53]

Table 1: Continued.

SNP ID	Position	Parameter association	Population	Adiponectin level (% change)	*P* value	Reference
		G allele associated with lower fasting insulin levels and lower HOMA-IR score	Nondiabetic Greek women			[54]
		G allele associated with higher TG, HOMA, fasting blood glucose, BMI and ALT, and lower adn levels; T allele associated with lower body weight	Chinese (NAFLD/metabolic syndrome)	28.68	.008	[55]
		GG associated with T2DM	Japanese			[56]
		G allele associated with T2DM (lower insulin sensitivity), lower adn, higher blood pressure, higher LDL and total cholesterol levels	Chinese (T2DM)	15.47	.01	[57]
		A allele associated with worse glucose tolerance and insulin sensitivity, but not adn levels	Caucasian Canadians (nondiabetic)			[51]
		G allele associated with BMI and waist circumference	Hispanic Americans			[58]
		GG carriers had higher risk of becoming hyperglycaemic/diabetic, associated with increase in BMI and WHR over 3 years	French Caucasian			[34]
		No difference in risk for T2DM or IR	Korean (diabetic/ nondiabetic)			[59]
		T allele and TG genotype associated with lower serum adn, no association with IR	Caucasians	25.17	.0008	[60]
		GT genotype associated with impaired glucose tolerance	Spanish			[61]
		G allele conferred higher risk of developing T2DM than TT genotype, particularly when combined with SNP +276 T allele	European/Canadian subjects with impaired glucose tolerance			[62]
		T allele associated with lower BMI and HOMA-IR	Japanese (nondiabetic)			[63]
		In obese subjects, serum cholesterol and waist circumference were lower in TG genotype than in TT genotype	Swedish women (obese/lean)			[64]
		No association with adn levels	Caucasian Italians			[32]
		No association with risk for coronary artery disease	Caucasian Italians (T2DM)			[65]
		No association with T2DM, BMI, or insulin sensitivity	Pima Indians			[24]
		G allele associated with coronary artery disease in T2DM patients	European Caucasians			[66]
		G associated with higher adn levels	French Caucasians		.01	[23]

Table 1: Continued.

SNP ID	Position	Parameter association	Population	Adiponectin level (% change)	*P* value	Reference
rs1501299	+276 G > T	T allele associated with obesity	African American men			[67]
		GG associated with T2DM, higher insulin resistance, and lower adn levels in subjects with higher BMI	Japanese	10.40	.01	[56]
		T allele associated with higher adn levels	Caucasian women	4.46	.0031	[39]
		T allele associated with central obesity and hyperglycemia	Indigenous Taiwanese			[68]
		T allele associated with lower adn levels, diastolic blood pressure	Finnish men	33.58	.001	[69]
		T allele associated with higher fasting insulin levels and higher HOMA-IR score, possible association with body fat	Greek women (nondiabetic)			[54]
		GG genotype associated with lower adn levels, impaired glucose tolerance	Spanish		.015	[61]
		SNP associated with higher rate of insulin resistance, higher n-6/n-3 LCPUFA ratio in plasma phospholipids	Normolipidaemic obese children			[70]
		T allele associated with severe obesity, but not adn	French Caucasians (obese/lean)			[31]
		TT genotype associated with lower CVD risk in diabetic patients, those without CVD had higher adn levels	American men (T2DM)	27.03	.0029	[71]
		T allele is an important determinant of CAD and lower adn levels in patients with early onset CAD (50 years of age or less)	Italian CAD patients			[72]
		T allele associated with higher adn	Caucasian and African American adolescents	4.95, 5.81	.05,.03	[40]
		G allele carriers had higher TG, higher small dense LDL, and smaller LDL particle size; GG had lower adn, higher HOMA-IR	Korean (nondiabetic)	18.90	.026	[73]
		No association with adn levels or hypertension	Japanese men (hypertensive/ normotensive)			[74]
		No difference in allele frequencies between diabetic and nondiabetic, no difference in risk of T2DM or insulin resistance	Korean (diabetic/ nondiabetic)			[59]
		No association with T2DM, BMI, or insulin sensitivity	Pima Indians			[24]
		TT genotype associated with lower risk of coronary artery disease in T2DM patients	Caucasian Italians (T2DM)			[65]

Table 1: Continued.

SNP ID	Position	Parameter association	Population	Adiponectin level (% change)	*P* value	Reference
		TT genotype associated with higher adn levels	Caucasian Italians		.032	[32]
		G allele, GT genotype associated with lower serum adn, no association with insulin resistance	Caucasians	13.70	.00005	[60]
		T allele associated with lower BMI and HOMA-IR	Japanese (nondiabetic)			[63]
		T associated with higher adn levels	French Caucasians		.01	[23]
rs1063538	+3228 C > T	T allele associated with higher adn levels	Caucasian women	24.97	.036	[39]
rs1063538	+3286	No association with T2DM, BMI, or insulin sensitivity	Pima Indians			[24]
	+10211 T > G	G allele associated with higher diabetes risk, higher BMI, and lower adn levels	Asian Indians		.007	[75]
rs12495941	G > T	T allele associated with lower adn levels	Chinese (hypertensive)		.0001	[43]
rs3774261	A > G	G allele associated with IR	African Americans			[76]
rs1656943 (rs822387)	T > C	C allele associated with higher adn levels	Hispanic Americans and African Americans	12.62	.003	[27]

−11377 G > C was a determinant of HOMA-IR, where CC homozygotes had significantly lower HOMA-IR scores [77]. There is evidence that the presence of the minor G allele decreases the affinity of the transcription factor Sp1 to its binding site within the *AdipoQ* promoter [78], and a recent study showed that this allele had altered DNA-binding activity, leading to lower basal and inducible *AdipoQ* promoter activity in mouse 3T3-L1 adipocytes [79]. The mechanism by which the C allele might contribute to disease remains unclear.

The silent +45 T > G SNP is strongly associated with detrimental health effects including lower adiponectin levels [55, 57], higher BMI and lower insulin sensitivity [34, 55], higher risk for developing hyperglycemia and T2DM [34, 52, 53, 56, 57, 62], and higher levels of blood lipids (triglycerides, LDL cholesterol, and total cholesterol) [55, 57]. In contrast, the T allele generally appeared to afford the carrier some protection, being associated with higher adiponectin levels [53] and lower body weight [55, 63]. A few studies obtained results that differed, and some found no significant associations with these parameters at all; however, the overall trends remained apparent even across such diverse populations as Iranians, Japanese, and European Caucasians [34, 52, 56]. The mechanisms by which these genetic variations exert effects on adiponectin levels and metabolic disease parameters have not been fully elucidated. Yang et al. [80] showed that the silent +45 T > G mutation may alter RNA splicing or stability, suggesting an allele-specific differential expression of adiponectin. It is thus possible that SNPs with no apparent biological significance may have an effect on gene expression, although in this case it is likely that SNP +45 is in linkage disequilibrium with some other functional genetic alterations, resulting in the difference in mRNA expression of its two alleles. Other research has indicated that the +45 T > G SNP is in linkage disequilibrium with the +276 G > T SNP and that the haplotype defined by the two together is strongly associated with many components of the metabolic syndrome [61, 62, 81].

The G allele of the +276 G > T SNP is primarily associated with lower insulin sensitivity and increased T2DM risk, lower adiponectin levels, and increased blood lipids. Conversely, many carriers of the T allele have higher adiponectin levels and a lower BMI. Two notable exceptions to this trend are the studies authored by Beebe-Dimmer et al. [67] and Bouatia-Naji et al. [31], in which the presence of the T allele corresponded with severe obesity. The first of these occurred in African American men, and so the conflicting results may be attributed to the racial composition of the populations studied. The second was a study of lean and obese French Caucasians. The authors suggest that while the higher adiponectin levels seen in the obese T allele carriers may protect them against insulin resistance and T2DM, hyperadiponectinemia may actually predispose these patients to weight gain due to the insulin-sensitizing effects of adiponectin, which could promote lipid uptake and storage [31, 82]. This mechanism may also explain why

some populations have higher adiponectin levels despite being in an obese state. The T allele also appears to be an important determinant of CVD risk; however, this may correlate directly with the tendency of T allele carriers to have increased adiponectin levels, as demonstrated in one study in which the diabetic participants with the TT genotype had lower risk of CVD, while those without CVD had higher adiponectin levels [71]. Several other studies identified the T allele as a determinant of cardiovascular risk [65, 72].

Overall, the magnitude of change in adiponectin levels varies considerably between studies. This is not surprising, since the studies examine populations that are very different in ethnicity, age, and health condition. However, it is worth noting that several studies show quite substantial changes in adiponectin levels and therefore provide convincing evidence that seemingly minute variations in the genetic code can produce large changes in adipokine levels, and thus significantly affect health status.

3.2. AdipoQ Nutrient-Gene Interactions. Subtle genetic variations can have a large impact on important obesity-related disease determinants, as demonstrated by many of studies discussed above. Individuals with SNPs in genes such as *AdipoQ* can be subject to greater sensitivity to dietary factors, due to the critical role adiponectin plays in maintaining metabolic balance. Several recent studies have investigated the nutrient-gene interactions that take place between dietary factors and *AdipoQ* SNPs. Pérez-Martínez et al. [83] investigated the influence of dietary fat on insulin resistance in C allele carriers of the −11377 G > C SNP in Caucasian men and women. Only men who were homozygous for the C allele had significantly lower IR after consuming monounsaturated (MUFA-) and carbohydrate-rich diets than after consuming an SFA-rich diet. In a population of European Caucasian ancestry with MUFA intake above the median, lower BMI and decreased obesity risk were observed in carriers of the −11391 A allele [84]. The +45, +276, and −11377 SNPs were examined in 363 subjects with impaired fasting glucose or newly diagnosed type 2 diabetes following a dietary intervention (replacement of cooked refined rice with whole grains and an increase in vegetable intake) and regular walking for 12 weeks without any medication. Fasting glucose levels declined in all genotype groups of the +45 T > G SNP, and TT homozygotes had increased adiponectin levels and lower HOMA-IR indexes [85]. In another study, obese Japanese women with the +276 SNP were placed on a low-calorie diet for 8 weeks. At the study conclusion, those with a GT or TT genotype had a greater decrease in waist circumference, and those with the TT genotype in the +45 SNP had lower plasma triglycerides. In the same population, the participants with CG and GG genotypes at SNP −11377 enjoyed a greater decrease in systolic blood pressure and fasting plasma glucose than those with CC [86]. Each of these studies used appropriate statistical testing to determine significant interactions between the gene polymorphisms and metabolic parameters. These findings correspond with the trends in metabolic disease discussed in the previous section.

4. Leptin

Leptin regulates body weight and energy expenditure, and plays important roles in the modulation of glucose and lipid metabolism, angiogenesis, immunity, and blood pressure homeostasis. Leptin is also a critical signalling molecule in the hypothalamus, where it influences appetite and satiety. The circulating levels of leptin correlate directly with adipocyte number and size [87], thus, leptin levels are elevated in obesity and are thought to exacerbate many of the negative effects of weight gain, such as contributing to the local inflammatory response [88] and creating a positive feedback loop for feeding behaviour through leptin resistance [89]. More details on the many roles of leptin in metabolic disease can be found in recent reviews [90–92].

The study of leptin began when mice homozygous for single-gene mutations in the leptin gene (*ob/ob*) and the leptin receptor gene (*db/db*) were identified [93]. The absence of leptin or its receptor leads to uncontrolled eating, and mice with either defect become massively obese. Treatment of *ob/ob* mice with leptin injections brings about a reduction in body weight to that of a normal mouse. For this reason, leptin was once believed to be the solution to the Western world's epidemic of obesity. Unfortunately, it was soon determined that such monogenic mutations occur very rarely in humans. In fact, severe obesity due to a single mutation in the leptin gene has been observed in only 12 human cases in the entire world [94]. It is now clear that multiple genes and gene variants are involved in the development of human obesity. SNPs in the human leptin gene (*Lep*) and the leptin receptor gene (*LepR*) can have a profound impact on body weight, insulin resistance and other metabolic disease parameters. The literature describing the effects of these SNPs is summarized in Table 2.

4.1. Leptin and Leptin Receptor Gene Variants: Risk for Obesity-Related Metabolic Disease. The *Lep* gene is located on chromosome 7q31 and encompasses approximately 20 kb. It contains 3 exons, the first of which is noncoding. Its sequence is highly conserved and contains very little reported variation. Only one leptin SNP, +19 G > A, has been investigated in detail for its effects on obesity-related metabolic disease. A recent study found that the A allele was significantly associated with lower body weight, lower BMI, lower circulating leptin levels, and consequently, a lower risk for obesity in Caucasian and African-American women [100]. Another reported that the presence of the A allele was linked to higher leptin levels and lower BMI in obese Caucasian females compared to GG homozygotes, suggesting that carriers of this allele may experience better sensitivity to satiety signals via the leptin protein [99]. Several other publications failed to find any significant associations between this SNP and BMI or blood lipid levels [96–98]. The *Lep* +19 A > G variant lies within the first untranslated exon of the gene, and it is not known how such an alteration might modify protein function. However, it is has been suggested that the *Lep* +19 A > G SNP is in disequilibrium with promoter region variation that may have an effect on gene transcription [100].

Table 2: SNPs in the Leptin (*Lep*) and Leptin Receptor (*LepR*) Genes.

SNP ID	Amino acid change	Nucleotide change	Parameter association	Population	Leptin level (% change)	*P* value	Reference
Leptin (*Lep*)							
rs4731427			SNP associated with weight and waist circumference in African Americans	Young adults (Caucasians, African Americans)			[95]
		+19G > A	No association with BMI, WHR, fasting glucose & insulin, lipids and leptin levels				[96]
			No association with waist girth, plasma triglycerides, HDL-cholesterol, glucose and systolic, and diastolic blood pressure	French Caucasian			[97]
			No association with waist-to-hip ratio, fasting leptin, total cholesterol, high-density lipoproteins, triglycerides	Italian Caucasian (obese/non-obese)			[98]
			No genotype associated with BMI, but A allele associated with higher leptin levels in obese patients	French Caucasian (obese/non-obese)	18.93	.001	[99]
			A allele in females associated with lower body weight, BMI and plasma leptin levels, lower risk of obesity	African Americans and Caucasians	6.68	.01	[100]
rs17151919			SNP associated with weight and waist circumference in African Americans and weight in Caucasians, waist circumference in Caucasian women	Young adults (Caucasians, African Americans)			[95]
rs28954369			SNP associated with weight, waist circumference in African Americans and weight in Caucasians, waist circumference in Caucasian women	Young adults (Caucasians, African Americans)			[95]
rs2167270			SNP associated with weight in Caucasians, waist circumference in Caucasian women	Young adults (Caucasians, African Americans)			[95]
rs7799039		G > A	A allele significantly associated with BMI	Caucasians			[101]
		−2548 G > A	G allele associated with overweight, and with lower leptin concentrations in men		17.46	.05	[102]
			A allele not associated with obesity	Spanish Mediterranean			[103]

Table 2: Continued.

SNP ID	Amino acid change	Nucleotide change	Parameter association	Population	Leptin level (% change)	*P* value	Reference
Leptin Receptor (*LepR*)							
rs1137101	Gln223Arg	A > G	G allele associated with BMI, WHR, leptin levels, and insulin levels	Asian Indians (diabetic/ nondiabetic)		.001	[104]
			G allele associated with higher BMI, fat mass, and serum leptin levels	Caucasian women (post-menopausal)	31.15	.0001	[105]
			GG genotype associated with BMI in nonsmokers	Brazilians of European descent (Caucasian)			[106]
			G allele associated with increased rates of obesity, higher BMI and % fat mass	Greek			[107]
			GG genotype had larger subcutaneous abdominal adipocyte size than AA, however, no difference in overall adiposity	Pima Indians			[108]
			G allele associated with insulin resistance	Caucasians			[109]
			GG phenotype associated with lean phenotype	Spanish Mediterranean			[103]
			GG and AG genotypes associated with increased risk of familial hypercholesterolemia, but not obesity, insulin resistance or other lipid parameters	Dutch			[110]
			G allele associated with increased rate of obesity	Brazilians (obese/non-obese)			[111]
			AA genotype was associated with increased total abdominal fat	Belgian Caucasian women (overweight and obese)			[112]
			No association with BMI, fasting insulin, HOMA-IR, serum leptin, or soluble leptin receptor levels	Japanese			[113]
			G allele associated with increased adiposity	Danish post-menopausal women			[114]
			GG genotype had lower blood pressure compared to AA	Swedish men (hypertensive/ normotensive)			[115]
			G allele associated with CRC risk	Czech (CRC patients)			[46]
			G allele associated with higher fat mass and BMI				[116]
			A allele associated with higher insulin, leptin levels, and body fat	Mexican adolescents	62.02	.001	[117]
			No association with BMI, WHR, fasting glucose & insulin, lipids and leptin levels				[96]

Table 2: Continued.

SNP ID	Amino acid change	Nucleotide change	Parameter association	Population	Leptin level (% change)	*P* value	Reference
			AA genotype had greater risk of developing T2DM	Finnish (impaired glucose tolerance)			[118]
			G allele associated with BMI, change in BMI over time				[119]
	Ser(T)343-Ser(C)	T > C	T allele associated with overweight and fat mass in women; C allele carriers more responsive to weight loss on a low calorie diet				[120]
		+70 T > C	C allele associated with fat mass in women				[120]
	Lys656Asn	G>C	G allele associated with higher lean and fat mass	Caucasians			[121]
			No association with obesity, BMI, or % fat mass	Greek			[107]
			C allele associated with increased hip circumference, total abdominal fat, and subcutaneous fat	Belgian Caucasian women (overweight and obese)			[112]
			C allele associated with higher fasting glucose and fasting insulin in postmenopausal women	Belgian Caucasian women (overweight and obese)			[122]
			No association with blood pressure or BMI	Swedish men (hypertensive/ normotensive)			[115]
			No association with blood pressure, serum glucose, insulin, or leptin levels	Mexican adolescents			[117]
	Arg109Lys	+5193 G > A	No association with BMI, WHR, fasting glucose & insulin, lipids and leptin levels				[96]
			AA genotype was associated with higher leptin levels in postmenopausal women	Belgian Caucasian women (overweight and obese)	14.99	.02	[112]
			A allele positively associated with BMI	Korean			[123]
			No association with BMI, fasting insulin, HOMA-IR, serum leptin, or soluble leptin receptor levels	Japanese			[113]
			No association with obesity, BMI, or % fat mass	Greek			[107]
			A allele associated with fasting insulin in postmenopausal women	Belgian Caucasian women (overweight and obese)			[122]

Table 2: Continued.

SNP ID	Amino acid change	Nucleotide change	Parameter association	Population	Leptin level (% change)	*P* value	Reference
			AA genotype had greater risk of developing T2DM	Finnish (impaired glucose tolerance)			[118]
			GG genotype had lower blood pressure and lower BMI compared to AA	Swedish men (hypertensive/ normotensive)			[115]
rs1045895			SNP associated with change in BMI over time				[119]

The *LepR* gene is found on chromosome 1p31, spans about 100 kb, and contains 20 exons. Numerous analyses of *LepR* SNPs have been published over the last decade, as the role of these genetic variants as determinants of adiposity and related conditions has become clear. The SNP Gln223Arg A > G has been studied extensively in a wide range of populations. The G allele is primarily associated with increased adiposity, BMI and percent fat mass, as well as higher circulating insulin and leptin levels. Larger adipocyte size has also been observed in individuals with the GG genotype. A couple of studies revealed varying results, with the G allele linked to a lean phenotype [103] and lower blood pressure [115], or no association whatsoever with weight-related parameters [96, 113]. Conversely, the A allele has also been found to be associated with total abdominal fat mass, increased insulin and leptin levels, and higher risk of developing T2DM [117].

The Lys656Asn G > C SNP was analyzed in several different populations, but no consistent trends were identified—both alleles are associated with increased fat mass in different ethnic groups [112, 121], whereas the C allele has also been linked to increased fasting glucose and fasting insulin [122]. Two studies also reported no association between this SNP and blood pressure, BMI, leptin levels, insulin and serum glucose [115, 117].

The A allele of the Arg109Lys G > A SNP is associated with increased T2DM risk [118], higher leptin levels [112], and higher BMI [123]. Several studies reported no association between this SNP and obesity-related disease parameters [96, 107, 113], while one study found the GG, but not AA, genotype to be linked to lower blood pressure and BMI [115].

Functional data on these polymorphisms is scarce, and the mechanisms by which the genetic variation influences metabolism and obesity are largely speculative at this point in time. The increased fat mass and leptin levels in many of the *LepR* SNP carriers points toward a possible change in binding affinity for the leptin receptor. The receptor functions in a dimeric form both in serum and at the cell surface. The genetic variations in the coding gene for the receptor may alter the ability of subunits to form dimers, leading to the phenotypic differences observed. Quinton et al. [105] measured the leptin-binding activity of the soluble leptin receptor in study participants who were carriers of the Gln223Arg SNP and found significantly higher activity in individuals homozygous for the G allele than for the A allele. These authors suggest the change in binding affinity might also result in an evolutionarily significant tendency to higher fat mass, contributing to the fixation of these alleles in human populations.

4.2. Gene-Nutrient Interactions with Lep and LepR. Most of the literature on gene-nutrient interactions involving leptin or the leptin receptor focuses on fetal nutrition and leptin levels in breast-feeding mothers. Recent evidence suggests that early prenatal and postnatal nutrition has an impact on susceptibility to chronic disease later in life. Leptin in breast milk has been identified as a key protective factor against several metabolic and physiological changes at an older age, such as obesity and related medical complications [124]. Several recent reviews on this topic are available [125, 126].

There is scant research on the interactions of leptin or leptin receptor gene SNPs with dietary factors. One study analyzed the effects of leptin receptor polymorphisms and PUFA consumption in relation to insulin resistance and metabolic syndrome [127]. The findings revealed that participants in the lowest median of plasma (n-3) PUFA and LCPUFA with the GG genotype of the rs3790433 SNP were at higher risk for hyperinsulinemia and insulin resistance, whereas in individuals with the same genotype but high plasma (n-3) PUFA and LCPUFA the risk of developing hyperinsulinemia and insulin resistance was effectively eliminated. Moreover, a high-plasma (n-6) PUFA profile accentuated the risk of these same conditions in GG homozygotes. The study concluded that homozygous carriers of this SNP may be predisposed to metabolic syndrome compared with the A allele carriers, especially if the plasma fatty acid profile was unfavourable. Another study assessed the influence of the *LepR* Lys656Asn polymorphism on the leptin response secondary to a low fat or low carbohydrate diet in obese people [128]. Leptin levels were significantly lower in the Lys656/Lys656 cohort on a low fat diet than on a low carbohydrate diet. The Lys656/Lys656 group also enjoyed a decrease in several obesity-related disease parameters (BMI, weight, fat mass, blood pressure, total cholesterol, triglycerides, blood insulin, and glucose) on a low fat diet, while significant changes in only BMI, weight and fat mass were observed in Asn656 carriers on the same diet. These studies indicate that polymorphisms

in the leptin receptor genes can play an influential role in the body's physiological response to diet. There is a need for more research in this important area.

5. Concluding Remarks

In summary, the current literature demonstrates that SNPs in the genes for adiponectin, leptin, and the leptin receptor can to a great degree influence the carriers' susceptibility to obesity and related complications. While epidemiological studies have reported associations between adipokine levels and metabolic disease parameters, the evidence compiled here provides a compelling argument for the causality of adipokine levels in disease. In many of the studies cited here, changes in adipokine levels were observed in individuals with gene polymorphisms, and thus, the change in adipokine levels precedes the occurrence of pathological conditions. Varied downstream effects on parameters of health are to be expected, since the adipokines examined here play diverse roles in many organ systems, as recently reviewed by DeClercq et al. [129]. The genetic variants included in this review by no means constitute an exhaustive list, and further investigation of adipokine SNPs and their impact on human health is warranted. Furthermore, population differences are also a factor in the strength of genetic determinants of disease. The gene-nutrient interaction studies discussed emphasize the role of diet in the modification of risk for developing metabolic disease. Future research in this field is needed to confirm and expand the findings presented here.

Abbreviations

adn:	Adiponectin
BMI:	Body mass index
CAD:	Coronary artery disease
CRC:	Colorectal cancer
CVD:	Cardiovascular disease
FSI:	Fasting serum insulin
HOMA-IR:	Homeostatic model assessment of insulin resistance
IR:	Insulin resistance
LCPUFA:	Long chain polyunsaturated fatty acid
LDL:	Low density lipoprotein
MUFA:	Monounsaturated fatty acid
PUFA:	Polyunsaturated fatty acid
SNP:	Single nucleotide polymorphism
T2DM:	Type 2 diabetes mellitus
WHR:	Waist-to-hip ratio.

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