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Exploring the complex relationship between HIF-1 (rs11549465) and *NFκB1* (rs28362491) variations and obesity (Review)

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Abstract. The prevalence of obesity is steadily increasing and it has emerged as a primary public and clinical health concern that considerably affects healthcare services. Obesity is expected to affect more than one billion individuals by 2030 worldwide. Hypoxia-inducible factor 1 (HIF-1) is an oxygen homeostatic molecule encoded by the HIF-1A gene. The HIF-1 rs11549465 mutation, which is linked to various diseases, influences nuclear factor kappa-beta subunit1 (*NFκB1*) transcription; this factor governs more than 200 target genes that are crucial for immune system regulation and is associated with morbid obesity, diabetic nephropathy, coronary artery disease and rheumatoid arthritis, specifically through *NFκB1* rs28362491 single-nucleotide polymorphisms. Obesity and being overweight pose widespread risks for chronic ecillnesses, such as diabetes, heart disease and types of cancer. This review selects HIF-1 and *NFκB1* genes because of their complex interplay in inflammatory responses and their significant involvement in hypoxia and inflammation. In this review, we focus on the significance of HIF-1 rs11549465 and *NFκB1* rs28362491 variations in obesity through the hypoxia pathway and inflammatory-induced obesity to support the current ongoing efforts in clarifying the causes of obesity, overweight and related issues.

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Contents

1. Introduction

Obesity is characterized by excessive fat accumulation in adipose cells and is typically identified by a body mass index (BMI) of ≥30 kg/m^2 (1). Ethnic-specific waist circumference cut-points, which are determined by sex and body lipid percentage through various body composition methods,

are used for overall and abdominal obesity assessments (2). Obesity and overweight are substantial risk factors associated with heightened mortality and morbidity throughout the lifespan of an individual (3). In women, these conditions serve as precursors to pregnancy-related diabetes and postpartum complications, which contribute to pediatric obesity (4). During puberty, obesity is a notable risk factor for illness and disability. The likelihood of mortality increases proportionally with BMI, that is, individuals with a low BMI (<18 kg/m^2) are expected to face an exceptionally high risk of diseases and death (5).

Physiological mechanisms of obesity. Insulin resistance, diet and inflammation-induced obesity primarily originate from excessive nutrient intake, malfunctioning adipocytes and tissue hypoxia (6). Hypoxia involves hypoxia-inducible factor (HIF-1) and other signaling molecules, which may stimulate the release of free fatty acids and inhibit glucose uptake in adipose tissues (7). Upon activation, nuclear factor kappa B (*NFκB1*) in the cytoplasm translocates into the nucleus and regulates numerous genes that encode cytokines, such as tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1) and IL-6. These cytokines play a crucial role in the inflammation of adipose tissues. Cytokines affect specific metabolic processes; in particular, IL-6 and TNF-α regulate glucose transporter type 4 and influence insulin-stimulated glucose uptake by inhibiting lipoprotein lipase (8).

Cellular and tissue responses to hypoxia, particularly in adipocytes, are a complex process. When subjected to hypoxia, adipocytes initially experience swelling, which increase their size. This phenomenon induces hypoxic conditions within the adipose tissue and potentially leads to the generation of new blood vessels through adipogenesis-derived angiogenesis when required (4). Following the crucial expansion of adipose tissue mass, the demand for cardiac output and blood flow in the vessels to the tissue increases to aid in responses against hypoxia (9).

Genetic studies on obesity and hypoxia. Genetic studies are important in understanding the relationship between hypoxia and obesity and elucidate the molecular mechanisms that connect the two conditions. Hypoxia could be a consequence of obesity, that is, obese individuals have lower rates of blood flow in adipose tissues and muscles than non-obese individuals. Elevated body mass index (BMI) can lead to an increase in red blood cells (RBCs), which may be attributed to hypoxia in obese individuals. Genetic analyses revealed the causal association between elevated RBCs and risk of type 2 diabetes (T2D), that is, RBCs may mediate the pathogenesis of obesity-induced T2D. Higher BMI has been linked to an increased risk of myocardial infarction (MI), highlighting the importance of identifying the genetic basis of obesity-related complications, such as T2D and MI (10-13). Understanding the genetic underpinnings of obesity within the context of hypoxia is crucial to advance scientific knowledge and develop personalized interventions for individuals at high risk. Genetic investigations, such as Mendelian randomization, provide valuable insights into the causal effects of obesity on various health outcomes, such as cardiovascular diseases. By decoding genetic factors that influence susceptibility to obesity under hypoxic conditions, researchers aim to identify novel targets for intervention and therapeutic strategies to address the complex interplay among genetics, hypoxia and obesity (10,12,13).

Blood flow decreases as the tissue size increases until angiogenesis occurs, leading to the development of new vessels. This process is instrumental in combating hypoxia (10). The progression of hypoxia is contingent on the elevation of inflammatory response levels within the hypoxic adipose tissue in obesity. Other contributors to inflammation development include oxidative stress and endoplasmic reticulum stress (4). The surge in obesity rates has a profound effect on global populations and adversely influences psychosocial, physical and professional well-being. In Malaysia, obesity is a significant contributor to the declining health status of the general population (11). The present review provided a basis to explore the intricate interplay of lifestyle, physical activity and genetic factors in obesity and elucidate diverse patterns of anthropometric measurements across various populations. Emphasizing the need for supplementary genetic studies, it aimed to contribute data that complement initiatives, such as the Human Variome Project (12) and the HapMap Project (13) and offer valuable insights for a comprehensive understanding of obesity.

2. Obesity

Obesity is characterized by excessive fat accumulation in adipose cells and often identified by BMI >30 kg/m^2 (14). Treatment and prevention play crucial roles in comprehensively understanding biological functions related to obesity and overweight (15,16). A high BMI may indicate overall inactivity, weakening muscles and reduced aerobic capacity. The association between obesity and functional limitations elevates the risk of diseases linked to high BMI and directly influences the likelihood of disability (17). Obesity is connected to certain health behavior and practices. A distinct relationship exists between smoking and body size; slimmer individuals are more likely to smoke, whereas obese individuals are more inclined to abstain from smoking (18,19). Cigarette smoking reduces body fat through various mechanisms, including decreasing caloric and fat intake and increasing metabolic rate and energy expenditure (20,21). Hormonal and neurological signals, which are orchestrated and processed in the brain, govern energy balance. The central nervous system (CNS) is influenced by leptin, a hormone released by adipocytes and present in specific quantities corresponding to the number of adipose tissues (22-24). Leptin binds to receptors in the CNS and activates neurons in the appetite control center of the brain. This interaction is pivotal in regulating food intake (25).

The global increase in obesity cases is a growing concern and it is estimated that it will affect more than one billion individuals by 2030 (26). Obesity has emerged as a significant public health issue and contributes to insulin resistance and associated comorbidities, such as metabolic syndrome, cardiovascular disease (CVD) and T2D (27). The prevalence of obesity has increased since the 1960s in advanced countries. In 1980, 2.9% of the United States population was extremely obese and 34.9% individuals were overweight (28). By 2000s, approximately half of the population had BMI >25 kg/m^2, with one-third having BMI >30 kg/m^2. The total economic cost of obesity in the United States is estimated at US$ 60 billion per year, a significant portion of which is attributed

Table I. Prevalence of obesity in the world according to WHO.

First author/s, year	Obesity in the world	(Refs.)
Chooi *et al*, 2019	>1.9 billion adults (18-year age) and older were overweight	(116)
Chooi *et al*, 2019	39% of men and 40% of women aged 18 or over living with overweight 13% living with obesity.	(116)
Bluher *et al*, 2019	38.2 million children under the age of 5 years were overweight or obese.	(117)
Wang *et al*, 2020	~770 million adults globally were affected by obesity	(118)
WHO, 2023	Overweight and obesity (BMI ≥25 kg/m^2) over 2.6 billion in 2020 compared with 1.9 billion in 2015	https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight

WHO, World Health Organisation.

to obesity-related T2D. The risk of obesity tends to increase significantly when calories and fat are widely accessible to populations (15).

The storage of surplus energy derived from the breakdown of food molecules that exceed the body's immediate needs, such as fat, is a significant evolutionary adaptation (29). Throughout history, humans have encountered diverse situations and periods marked by food scarcity and excess nutritional resources (30). Developed countries benefit from advanced technologies, food preservation techniques, efficient transportation, rapid westernization and urbanization, to facilitate extensive and cost-effective food storage (31). This practice has diminished the likelihood of returning to eras characterized by food scarcity and minimal nutritional value (32). The global statistics indicate that more than 1.9 billion adults worldwide are classified as overweight; according to the World Health Organisation (WHO) in 2016 (33), 13% of individuals were obese. The prevalence of obesity worldwide is detailed in Table I.

According to the estimates of WHO, the number of individuals with diabetes in Malaysia is projected to increase to 2.48 million by 2030 compared with 0.94 million in 2000, representing a substantial increase of 164%. This surge in diabetes cases is associated with the increasing prevalence of obesity (34,35). The likelihood of individuals with diabetes experiencing cardiovascular disease is two to three times higher than that of non-diabetics. Obesity has emerged as a primary public and clinical health concern that considerably affects healthcare services in Malaysia (35). Individuals have decreased physical activities and most of them engage in sedentary behavior, such as using cars and public transport, including trains and buses and relying on technological innovations, such as television, smartphones and computers (36). The proliferation of Internet resources has contributed to a sedentary lifestyle characterized by reduced physical activity and increased time spent on sedentary behavior, such as watching TV, sitting at work or driving. This shift in lifestyle is linked to an elevated risk of obesity and overweight (37).

3. Role of genetics in obesity

The genetic pattern of obesity is subdivided into three types; inclusive monogenic syndromic obesity (Mendelian), monogenic non-syndromic obesity and polygenic obesity (38). Mendelian obesity depends on abnormalities in chromosomes (X-linked) and is polygenic. Monogenic is not common and is caused by high-risk variants. Polygenetic obesity is multifactorial; variants have minimal effects individually and can synergistically cause obesity (39).

A number of genes and their mutations can cause obesity phenotype in animals and humans. These genes are components of energy balance system regulation. For example, leptin (OB protein) is a hormone from adipose tissues and has a number of physiological roles; it involves brain receptors that manage energy expenditure and food intake (3). The levels of leptin depend on body fat fluctuation, which may decrease or increase food intake volume (15). Humans become greatly obese if mutations occur in the OB protein or leptin in the hypothalamus, peripheral tissues and brain. Any damage in hypothalamus neurons with leptin receptors can cause massive obesity (40).

Syndromic obesity is distinguished by the presence of various associated clinical phenotypes, including organ-specific developmental abnormalities, intellectual disability (ID) and dysmorphic features. Over 25 syndromic forms of obesity have been identified, such as Bardet-Biedl and Prader-Willi syndrome (41). Non-syndromic obesity is primarily characterized by genetic associations with leptin/melanocortin disorders and results in hyperphagic obesity (42). Polygenic obesity involves the collective effect of multiple genes. For instance, fat mass and obesity-associated protein (FTO) are significant genes in polygenic obesity (43).

4. Role of hypoxia in obesity

Hypoxia is associated with decreases in the normal levels of tissue oxygen concentration. It may cause cell death if it is prolonged or severe (44). Scientists study hypoxia because of its disruption in responses to radiotherapy. Radiation can destroy target cells by producing free radicals in the hypoxic tissue and inducing cell death (45). Tumor cells can survive and continue proliferating within hypoxic areas in comparison with cells in perfusion-limited areas (46). Nordsmark *et al* (47) fabricated oxygen electrodes related to a tumor oxygen supply and demonstrated that hypoxia is associated with human

tumors. They proved the association between poor survival metastasis and low oxygen tension in patients suffering from tumors of the breast, cervical or neck and head (48).

Hypoxia can activate a number of genes and transcription factors, such as hypoxia-inducible factors (*HIFs*) and nuclear factor kappa subunit B (*NF-κB*), which play a central role in the activation of other genes and in the release of several inflammatory chemokines and cytokines (49,50). Cytokines have important roles in inflammation responses, such as macrophage permeation into adipose tissues. Yin *et al* (7) focused on the production of chronic inflammation caused by obesity-induced hypoxia. Hypoxia reduced free fatty acid (FFA) uptake and lipolysis was increased in adipocytes in adipose tissues; hence, hypoxia has a role in increasing chronic inflammation.

The diagnostic or prognostic roles of hypoxia are related physiologically (51). A number of studies examined cellular responses and molecular signaling pathways under acute and severe hypoxia. Several pathways are involved in hypoxia and cells have various biological responses to hypoxic conditions. The first pathway involves the transition of hypoxic cells from aerobic to anaerobic metabolism (52). Hypoxia enhances tyrosine hydroxylase synthesis in neural cells, contributes to catecholamine production and stimulates the production of erythropoietin by renal cells, leading to increased red blood cell production and enhanced hemoglobin oxygen transport (53). Another pathway for hypoxic response is the production and activation of growth factors that induce angiogenesis; this pathway induces the production of new blood vessels during acute and chronic vascular diseases, cancer, pulmonary disease and tissue injuries (54).

In cancer, the affected tissue becomes hypoxic depending on the level of angiogenesis and may die; tumor cells exhibit adaptive and genetic changes, which allow them to proliferate and survive in the hypoxic microenvironment (55). Human tumors can grow around blood vessels and utilize oxygen molecules 180 μm away from the blood vessels, which is the maximum distance for oxygen molecules between the capillary and the cells (55,56).

Chronic hypoxia is caused by the uncontrolled production of tumor cells to outgrow the limited oxygen supplied by blood. Another type of hypoxia, known as 'perfusion-limited' or 'acute' hypoxia, occurs when blood vessels are blocked and can cause reverse blood flow (57). Blocked vessels can be treated by inverting the supply of oxygenated blood to the hypoxic tissue; this phenomenon, also called oxygenation injury, can increase the number of free-radical molecules and activate stress-response genes and tissue damages (58). Continued hypoxia occurs in individuals who stay in high-altitude areas and conditional hypoxia occurs in patients with sleep apnea who have blocked airways while sleeping, leading to a rapid decline in blood oxygen pressure in a process called hypoxemia (59).

Obese individuals exhibit augmented size and volume of adipose tissues and fat accrual within white adipose cells induces chronic hypoxia in the adipose tissue. This phenomenon occurs because cells with expanded size have inadequate oxygen provision (60,61). Adipose cells respond to hypoxia differently compared with other cell types. The nature and pace of the response is contingent on the rate of decline in oxygen concentration (62). The initial effect of hypoxia on adipose tissues involves the enlargement of adipose cells. However, the tissue requires more oxygen than that currently available, thereby increasing the hypoxia levels (10). Adipose tissue consists of macrophages, mast cells, dendritic cells and vascular endothelial cells. Macrophages are important in the primary inflammatory reaction and prevent tissues from developing obesity (63). Obesity-induced inflammation is recognized by the elevated inflammatory level in adipose tissues and plasma and macrophages in adipose tissues are implicated in inflammation and obesity (64).

HIF-1 is the main transcription factor in response to decreases in oxygen rate. Other crucial transcription factors that contribute to adipose tissue responses to hypoxia are glucose transporter 1, leptin, vascular endothelial growth factor (VEGF), matrix metalloproteinase-2, matrix metalloproteinase-9, IL-6, IL-4 and plasminogen activator inhibitor-1 (65). The role of hypoxia is not yet fully understood but has been discovered in a number of essential processes, such as insulin resistance, glucose intolerance and inflammation with induced angiogenesis (66). A study reported on other nuclear partners involved in oxygen level pathways [HIF-2, NF-κB, peroxisome proliferator-activated receptors (PPARγ) and cAMP response element binding (CREB)] (67).

5. Role of inflammation in obesity and lipid metabolism

The major reasons for insulin resistance, diet-induced obesity and inflammatory-induced obesity are excess nutrients, adipocyte dysfunction and tissue hypoxia (66). Hypoxia involves hif-1α and other signaling molecules that might promote free fatty acid release and prevent glucose uptake in adipose tissues (68). Hypoxia induces the expression of *NFκB1*, which regulates a number of genes that encode cytokines, such as TNF-α, IL-1 and IL-6 and has an important role in adipose tissue inflammation (6). Metabolic processes, such as lipoprotein lipase inhibition by IL-6 and TNF-α, are affected. TNF-α also regulates insulin-stimulated glucose uptake via glucose transporter 4 (69). A strong association has been found between obesity and chronic inflammatory response and it is characterized by the management of pro-inflammatory signaling pathways and uncontrolled production of adipokines, which induces the expression of biological markers of inflammation (70). Inflammation affects lipids, energy metabolism and glucose in adipose tissues during obesity (71). Various pathways associated with obesity contribute to inflammation. Examples include the activation of protein kinase C or JNK by fatty acid derivatives (such as ceramide or diglycerides), activation of Toll-like receptor (TLR) 4 by fatty acids, induction of endoplasmic reticulum stress, high levels of reactive oxidative species and activation of macrophages by adipocyte death (72). The catabolic and anabolic pathways for lipid storage require specific transporters, such as chylomicron for diet in lipids, triglycerides (TG), very low-density lipoprotein and albumin (73).

Physical activity reduces percentage and mass of body fat, visceral and subcutaneous adipose tissue, BMI and TG levels and increases high-density lipoprotein cholesterol (74). Decreases in triglycerides and total cholesterol affect body shape, especially BMI and fat mass (2). Adipose tissue is

the main endocrine organ that generates hormones, such as resistin, adiponectin, leptin, apelin and acute phase serum amyloid A (A-SAA); it controls body metabolism and regulates whole-body components and weight (75). A-SAA has a necessary role in fat mobilization and systemic inflammation and produces inflammatory markers, such as IL-8, which are associated with a number of diseases, including atherosclerosis and insulin resistance. Other inflammatory markers that have an important role in metabolic diseases are TNF-α and IL-6, which result from oxidative stress and hypoxia (76).

The association between metabolic syndrome and obesity is linked to an increased risk of T2D and cardiovascular diseases. A key component of metabolic syndrome is insulin resistance, which is accompanied by dysregulation of glucose and blood pressure and altered lipid metabolism (77). Abdominal obesity is an important component of metabolic syndrome; determining fat distribution in obese body and its effects on body health is important (78). Abdominal hip and waist circumference and their ratio (W/H) are used to classify obesity into ganoid (peripheral) and android (central) types. Peripheral fat plays a main role in metabolic risk processes and these indices are used to differentiate metabolic syndrome and obesity. The mechanisms underlying the effects of metabolic risk on obesity are not fully understood and all fat indices are only predictors of diabetes and heart diseases (79).

6. HIF and obesity

HIF-1. is crucial to maintain oxygen homeostasis and regulate biological processes, including protein translation, post-translational modification, gene transcription, angiogenesis, glucose, energy metabolism, erythropoiesis, iron homeostasis, cell proliferation, survival, cell death and autophagy (71-73). The *HIF*-1 activator complex activates several hypoxia-responsive genes, such as hypoxia-response elements (HRE), VEGF and nuclear factor kappa βeta (*NFκB1*) (80). The *HIF*-1 activator complex is composed of two protein subunits: i) HIF-1 aryl hydrocarbon receptor nuclear translocator (*HIF*-1β/ARNT); and ii) *HIF*-1α, which are present in cells but activated only under hypoxia. The *HIF*-1α subunit is synthesized and degraded under normoxic situations while it accumulates upon exposure to lack or low oxygen levels (81). According to the description of *HIF* and its regulatory functions, these genes produce chemokines and interleukins, such as TNF-α, which can activate transcriptional factors, such as *NFκB1* (38).

HIF-1 gene. The *HIF-1* gene is located in chromosome 14 at locus q23.2 and comprises 14 exons and 13 introns with a direct orientation. The chromosome assembly reveals the initiation and termination points of the *HIF-1* gene at 61,695,401 and 61,748,259 base pairs, respectively, encompassing a total size of 456,821 bases and consisting of 152,273 codons for translation (82,83).

Single-nucleotide polymorphisms (SNPs) in HIF-1 gene. Numerous polymorphisms within the HIF-1 gene have been identified because of their significant involvement in hypoxia and angiogenesis. A selection of these SNPs is provided in Table II.

Table II. SNP of *HIF-1* gene.

First author/s, year	SNP	Alleles	(Refs.)
Nagy *et al* 2009	rs11549465	C/T	(85)
Lu *et al* 2012	rs2057482	C/T	(105)
He *et al* 2011	rs17039192	C/T	(114)
Bradbury *et al* 2017	rs9340	C/T	(119)
Emanuele *et al* 2010	rs2010963	C/G	(120)
Rockwell *et al* 2009	rs1870377	A/T	(48)

SNP, single nucleotide polymorphisms.

Association of HIF-1 (rs11549465) variant with obesity. HIF-1 is associated with various reported SNPs, which play crucial roles in different diseases and pathways (11,84). These SNPs are implicated in conditions such as elite endurance in athletes, T1 and T2D, prostate cancerand knee osteoarthritis (85). One specific *HIF-1* gene variant, rs11549465, is located at 61,740,839 bp, approximately 45,438 bp upstream of the translation start site of the HIF-1 gene. This variant has the T allele as an alternative and the C allele as a reference allele (11). The characteristics of the rs11549465 variant are summarized in Table III.

The present review investigated the rs11549465 (Pro582Ser) variant of HIF-1 because of its significance and role under specific conditions, considering the sample type and population. Table IV outlines diseases associated with the HIF-1 (rs11549465) variant.

A study explored the link between HIF-1-α gene and T1 and T2D in a Caucasian (Hungarian) population. The findings revealed a statistically significant reduction in TT and CT genotypes, indicating that the T allele had a protective effect against T2D and T1D (85). Döring *et al* (84) discovered the association between the HIF-1 variant and maximum volume of oxygen ($V^{\cdot}O_2$) before and after workout training of elderly Swedish men. The homozygous pro variant of HIF-1A (Pro582Ser) was implicated.

A pilot study investigated the polymorphism of the HIF-1A gene rs11549465 variant and demonstrated its potential contribution to the development of knee osteoarthritis in Mexico (82). A significant association was found between the HIF-1 gene polymorphism rs11549465 and the risk of osteoarthritis, particularly in the C allele. This variant is known to protect articular cartilage in the population (80). In a similar study in Georgia that focused on angiogenesis genes with prostate cancer, HIF-1A rs11549465 SNP, also known as P582S, could significantly reduce the risk of developing prostate cancer (86). A study, 'The association of (*HIF-1*A rs11549465, *ACE* I/D, *PPARA* intron 7 G/C, *NOS*3 -786 T/C, *PPARGC1B Ala203Pro* and *PPARG Pro12Ala*) gene polymorphisms with athlete status in Ukrainians population' (87) found that *NOS3* T, *HIF-1A* Ser and *PPARG* Ala alleles are related to the strength of Ukrainian athletes.

Heterozygosity of HIF-1 (rs11549465) variant. Heterozygosity is the percentage of heterozygous genotypes compared with the whole sample of genotypes and reflects the entire

Table III. *HIF 1* gene (rs11549465) variant characterization.

First author/s, year	Characterization	rs11549465	(Refs.)
Nagy *et al*, 2009	Position	61740839 (Chromosome assembly)	(85)
Nagy *et al*, 2009	Risk Allele	'T'	(85)
Nagy *et al*, 2009	Normal Allele	'C'	(85)
Nagy *et al*, 2009	Chromosome	14	(85)
Nagy *et al*, 2009	Orientation	Plus (Direct)	(85)
Nagy *et al*, 2009	Stabilization	Plus (Direct)	(85)
Nagy *et al*, 2009	Reference	GRCh38.p7 Genome reference consortium human build 38 patch release 12	(85)

Adapted from NCBI website: https://www.ncbi.nlm.nih.gov/snp/rs11549465/

Table IV. Disease association of *HIF* 1 variant (rs11549465).

First author/s, year	Disease	Association	Method	(Refs.)
Nagy *et al*, 2009	Type 1 and type 2 diabetes (hypoxia)	Significant	Restriction fragment analysis (RFLP) and reverse transcription PCR	(85)
Döring *et al*, 2010	Hypoxia-inducible factor-1alpha gene in elite endurance athletes	Significant	Reverse transcription PCR	(84)
Fernández-Torres *et al*, 2015	Development of knee osteoarthritis	Significant	Reverse transcription PCR	(121)
Jacobs *et al*, 2008	Angiogenesis and Prostate Cancer	Significant	Reverse transcription PCR	(86)
Drozdovska *et al*, 2013	Athlete status in Ukrainians (Hypoxia)	Significant	PCR	(87)

heterozygosity of the population (88). The HIF-1 (rs11549465) variant has been studied in different populations to determine the level of heterozygosity. The highest level of heterozygosity has been reported in the Sub-Saharan African population. Table V summarises the heterozygosity of the HIF-1 (rs11549465) variant in different populations.

7. NF-κB and obesity

NF-κB is a transcription factor that comprises a protein complex including *NFκB1* (p50/p105), NFKB2 (p52/p100), RelA (p65), RelB and c-Rel. *NFκB1* plays a crucial role in cellular responses to hypoxia, oxidative stress, cytokines, ultraviolet irradiation, free radicals and bacterial antigens (89). *NFκB1*, an IκB-bound compound in the cytoplasm, is inactive under normal conditions. *NFκB1* can be activated through two pathways, namely, canonical (classical) and non-canonical (alternative) (90). The common regulatory step in both pathways is the activation of an IκB kinase (IKK) compound, a sensing protein termed *NFκB1* essential modulator (NEMO). As such, *NFκB1* dimers are activated through IKK-mediated phosphorylation-induced degradation of the IκB inhibitor, which leads to the entry of the *NFκB1* dimers to the nucleus from the cytoplasm to activate specific target genes (91). *NFκB1* is a transcription factor localized in the cytoplasm of every cell and is translocated to the nucleus upon activation. *NFκB1*/IκB regulates the expression of more than 200 target genes (for example, TNF-α, IL-1 and IL-6) and most of which are related to immune responses (91).

NF-KB 1 gene. The *NFκB1* gene is located at chromosome number 4 at locus 4q24. The gene has 24 exons and 23 introns with direct orientation. The chromosome assembly shows the starting gene at 102,501,329 base pair and ends at 102,617,302 base pair with a total size of 115,974 base pairs and 38,658 codons for translation (92,93).

SNPs in NFκB1 gene. NFκB1 exhibits cellular responses to the body's reaction to stimuli, such as hypoxia, oxidative stress cytokines, ultraviolet irradiation, free radicals and bacterial antigens (94). It regulates more than 200 target genes involved in immune regulation. A number of polymorphisms are reported in the *NFκB1* gene related to inflammation and symptomatic diseases, such as certain types of tumor (95). Table VI summarizes some of these polymorphisms.

Evidence suggests that polymorphisms in the promoter region can affect transcription regulation and result in expression and differential expression of the *NFκB1* gene (96,97).

Table V. Studies of *HIF 1* gene rs11549465 heterozygosity (dpSNP database, 2018, https://www.ncbi.nlm.nih.gov/snp/).

ss Polymorphism	Population	Heterozygosity, %
ss1351283416	EAS	4.5
	EUR	10.0
	AFR	3.2
	AMR	8.6
	SAS	11.9
ss1691508589	EXAC	9.5
ss226605360	Pilot-1-YRI-low-coverage-panel	11.9
ss236568433	Pilot-1-CEU-low-coverage-panel	8.9
ss242997447	Pilot-1-CHB+JPT-low-coverage-panel	2.5
ss24616754	AFD-EUR	12.5
	AFD-AFR	13.0
	AFD-CHN	12.5
ss342388769	ESP-Cohort-Population	15.0
ss48419058	AGI-ASP Caucasian	15.7
ss491688417	CSAgilent	20.9
ss66538519	R24	6.0
ss69159438	HapMap-CEU	15
	HapMap-HCB	4.4
	HapMap-JPT	4.4
	HapMap-YRI	5.0
ss7689800	HapMap-CEU (European)	13.2
	HapMap-HCB (Asian)	4.6
	HapMap-JPT (Asian)	6.9
	HapMap-YRI (Sub-Saharan African)	5.3
HIF-1 (rs11549465) heterozygosity average		16.3±-0.234%

EAS, East Asian; EUR, European; AFR, African; AMR, mixed American; SAS, South Asian; EXAC, Exome Aggregation Consortium; CSAgilent, European from ClinSeq project; R24, San Francisco Bay Area; AFD-CHN, Han Chinese.

Association of NFκB1 (rs28362491) variant with obesity. The *NFκB1* gene (rs28362491) variant is located between 102500998 and 102501001 base pair as four base pairs in the chromosome 4 assembly, with the ATTG insertion allele as an alternative allele or the deletion of the ATTG allele as a reference allele.

A number of variants of the nuclear factor-kappa β 1 (*NFκB1*) gene have been reported, but the present review focused on the *NFκB1* (rs28362491) variant only given its roles in a number of diseases and conditions, such as diabetic nephropathy, morbid obesity, coronary artery disease, rheumatoid arthritis and acute myeloid leukemia. Table VII summarizes previous studies on this variant and its association in different populations.

Gautam *et al* (98) conducted a study on 'The association of *NFκB1* gene (rs28362491) SNP with levels of inflammatory biomarkers and susceptibility to diabetic nephropathy in Asian Indians'. The *NFκB1* variant rs28362491 was significantly associated with increased levels of urinary monocyte chemoattractant protein-1 and plasma TNF-α, thereby increasing the risk of diabetic nephropathy. The -94 ATTG Ins/Ins variant might be related to an increased risk of developing nephropathy among Asian Indians (98). Another study investigated the relationship between *NFκB1* and TLR2 variants with the risk of morbidity obesity in the Turkish population. The insertion allele, especially Ins/Ins of the (rs28362491) variant genotype, was significantly higher in patients with morbidity obesity than in the control group (99). Yang *et al* (100) studied 'the association between *NFκB1* gene rs28362491 variant and coronary artery disease (CAD) in the Chinese population, especially in Han and Uyger women'; the frequency of (rs28362491) variant genotypes was significantly different between CAD and control subjects. The *NFκB1* Del\Del genotype of SNP rs28362491 has been proposed as a new genetic marker for CAD in the Chinese population.

Another study in Spain determined the relationship between the risk of coronary heart disease (CHD) and the *NFκB1* variant in Caucasian patients with rheumatoid arthritis (RA); the result showed that the Ins/Del genotype of the *NFκB1* gene (rs28362491) variant is associated with CHD in patients with RA (101). In addition, the frequencies of the II (Insertion/Insertion) genotype in patients with VSD and ASD were significantly higher than those in controls; hence, the *NFκB1* rs28362491 polymorphism in the promoter region is associated with CHD (102).

8. Relationship between *HIF* 1 and *NFκB1* SNPs and their association with diseases

SNPs in the HIF-1A gene are linked to several diseases; for example, rs11549465 is linked to multiple types of cancer, including colorectal, gastric, prostate, oral, breast, lung and renal cell carcinoma (103). Preeclampsia is linked to (s11549467) (104). In patients with aggressive hepatocellular carcinoma, rs2057482 predicts clinical outcomes (105). Chronic obstructive pulmonary disease, CVD, skin disorders, diabetic complications, preeclampsia, T1 and T2D, lumbar disc degeneration and other conditions have been linked to 1772 C/T and 1790 G/A polymorphisms (103-105). Studies have examined the relationships between these SNPs in the HIF-1A gene and various disorders and emphasized the significance of genetic differences in determining disease risk. rs230530, rs230529, rs230525, rs35680095, rs230494, rs170731, rs230528 and rs4698858 are found in the *NFκB1* gene; they are related to several diseases, including multiple myeloma, severe influenza A, atopic asthma, lung disease, cytokine modulation, liver cancer, alcohol addiction and inflammatory reactions in lymphedema following breast cancer therapy (106-108). *NFκB1* polymorphisms can affect the risk and severity of several diseases by altering immunological responses and gene expression. Further investigation is required to elucidate the influence of these SNPs on illness susceptibility and progression.

Table VI. SNP of the *NFκB1* gene.

First author/s, year	SNP	Alleles	Genotypic assembly location	Location	(Refs.)
Zhou *et al*, 2009	rs28362491	±ATTG	102500998	Promoter	(122)
Bauman- *et al*, 2019	rs4648090	A/G	102605911	Intron variant	(112)
Chen *et al*, 2015	rs4648068	A/G	102597148	Intron variant	(123)
Chen *et al*, 2015	rs4648065	C/T	102596306	Intron variant	(123)
Bauman-Fortin *et al*, 2019	rs230511	A/G	102553611	Intron variant	(112)
Curtin *et al*, 2010	rs4648110	A/T	102612664	Intron variant	(124)

SNP, single nucleotide polymorphisms.

Table VII. Disease association of *NFκB1* (rs28362491) variant.

First author/s, year	Disease	Method	Signification	(Refs.)
Gautam *et al*, 2017	Inflammatory biomarkers and susceptibility to diabetic nephropathy	PCR-restriction fragment length polymorphism and ELISA	Significant	(98)
Soydas *et al*, 2016	Morbid obesity	PCR-restriction fragment length polymorphism	Significant	(99)
Yang *et al*, 2014	Coronary artery disease	Standard reverse transcription PCR	Significant	(100)
López-Mejías *et al*, 2012	Cardiovascular disease in patients with rheumatoid arthritis	Reverse transcription PCR	Significant	(101)
Zhang *et al*, 2013	Congenital heart disease	PCR polyacrylamide gel electrophoresis	Significant	(102)
Rybka *et al*, 2016	The risk of acute myeloid leukemia	reverse transcription PCR	Significant	(125)
Pereire *et al*, 2021	Sarcopenia	PCR	Significant	(126)

9. *HIF-1* gene (rs11549465) and *NFκB1* gene (rs28362491) variations

HIF-1 and *NFκB1* are not the only genes linked to obesity. Human obesity has been linked to variations in genes relevant to innate immunity. The following genes have been linked to obesity: Turkish TLR2 rs5743708 is related to an increased risk of morbid obesity; Argentinian TLR4 rs11536889 protects against overweight; TLR4 rs4986790 + rs4986791 is involved in enhanced visceral and total body fat in in habitants of Caucasus mountains; TLR4 rs1928295 is related to a high BMI in Europeans; TLR5 rs5744168 protects against obesity among Saudi Arabians and leads to low BMI; LRRFIP1 rs11680012 is linked to higher levels of abdominal obesity and inflammatory indicators in Canadians; CD14 rs2569190 lead to a high BMI in Koreans; NLRC3 rs758747 is related to high obesity rates in Pima Indians, Pakistanis and Europeans; NLRP3 rs10754558 protects Brazilians against obesity; and FFAR4 rs116454156 indicates high probability to be obese among Europeans. The selection of the rs11549465 SNP in the HIF-1 gene and the rs28362491 SNP in the *NFκB1* gene was based on their well-documented roles in inflammation-induced obesity and their associations with various diseases and conditions, including morbid obesity, diabetic nephropathy, coronary artery disease and rheumatoid arthritis. These SNPs have been extensively studied and are significantly associated with different health outcomes, particularly obesity (109,110). The present review aimed to provide focused analysis of the intricate relationship between these SNPs, obesity and related inflammatory and metabolic processes. Additionally, it highlighted the importance of further research on these variants in diverse populations and geographical locations to broaden our understanding of their effect on obesity and related conditions. By discussing the two SNPs, it is intended to lay a foundation for future studies to delve deeper into genetic mechanisms contributing to obesity. The present review recognized the importance of expanding the investigation to include additional genetic variations and pathways in future research endeavors.

10. Molecular network involving HIF-1 and *NFκB1*

The molecular network involving HIF-1 and *NFκB1* encompasses a complex interplay of signaling pathways and

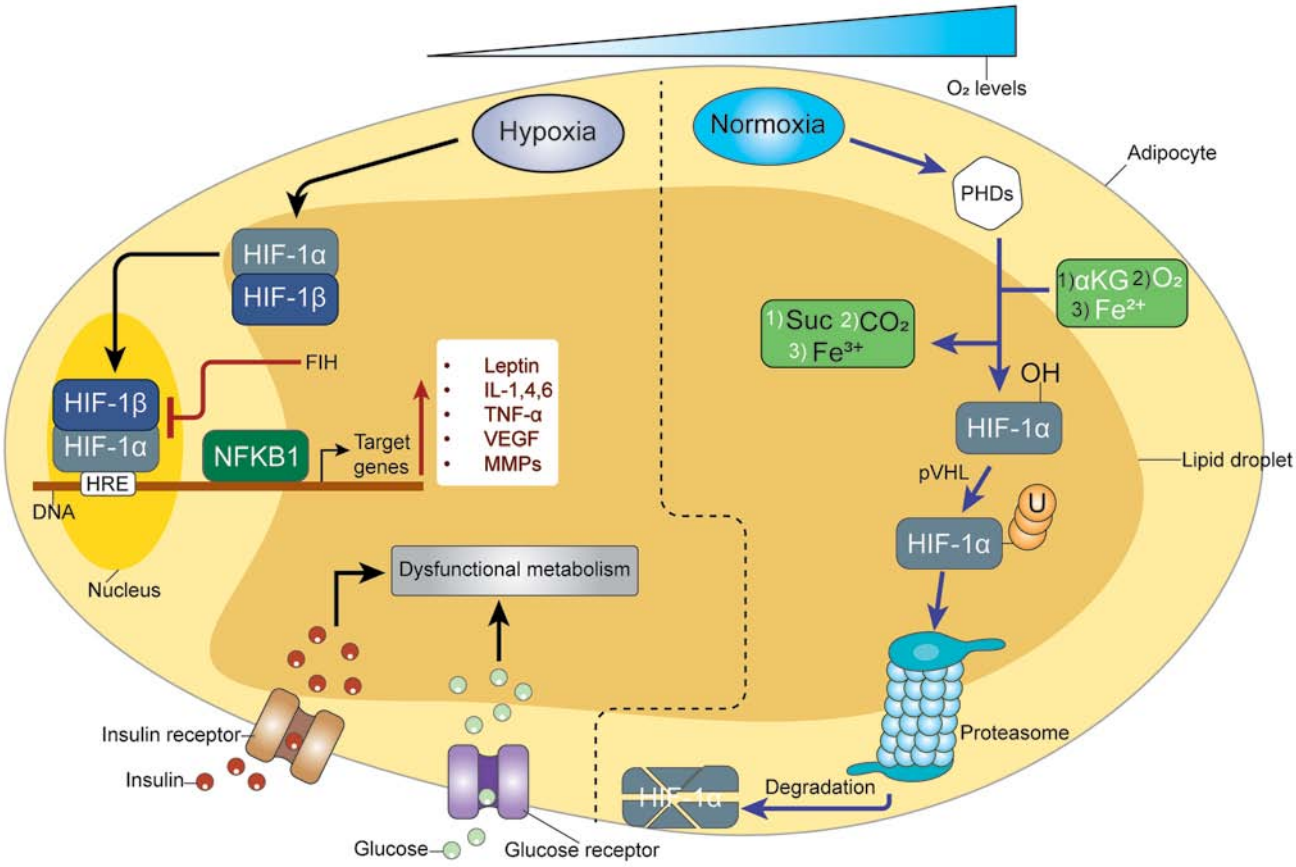

Figure 1. Possible association between diet-induced obesity and inflammation-induced obesity pathway [variants in the *HIF-1* gene (rs11549465) and *NFκB1* gene (rs28362491)] as the combination of two pathways. *NFκB1*, Nuclear Factor-κ β 1; VEGF, vascular endothelial growth factor; HRE, hypoxia-response elements; HIF, hypoxia-inducible factor; HIF-1β/ARNT, HIF-1 aryl hydrocarbon receptor nuclear translocator; FIH, factor-inhibiting HIF; PHDs, prolyl hydroxylases.

regulatory mechanisms that orchestrate cellular responses to various stimuli, including hypoxia and inflammation. HIF-1 and *NFκB1* are pivotal signaling molecules that interact with a myriad of other proteins, transcription factors and regulatory elements to modulate gene expression and cellular functions (111). Under hypoxic conditions, HIF-1 plays a crucial role as a master transcriptional regulator and controls adaptive responses to oxygen deprivation by activating genes involved in angiogenesis, glycolysis and cell survival. HIF-1 collaborates with proteins, such as HIF-1β and coactivators, such as p300/CBP, to form active transcriptional complexes that bind to HREs in target gene promoters. This activation leads to the upregulation of genes crucial for tissue protection and adaptation, including those involved in metabolically adapting tissues to oxygen deprivation and anaerobic ATP synthesis. HIF stabilization during hypoxia can dampen tissue inflammation and promote repair processes, highlighting its significance in managing various conditions, such as cancer and chronic diseases (112). The molecular network involving HIF-1 and *NFκB1* exhibits a complex interplay with mutual regulation and crosstalk between their signaling pathways. Hypoxia-induced stabilization of HIF-1 can affect *NFκB1* activity through various mechanisms, including direct protein-protein interactions or regulation of shared target genes involved in inflammatory responses. Inflammatory signals mediated by *NFκB1* can influence HIF-1 activity through pathways involving reactive oxygen species or cytokines. This intricate relationship between HIF-1 and *NFκB1* is crucial under various conditions, such as cancer, inflammation and immune responses, thereby highlighting the importance of understanding their interplay for potential therapeutic interventions (113).

HIF 1 involves several biological activities, including post-translational modification, gene transcription, protein translation and oxygen molecule homeostasis. The transcriptional factor HIF-1 is currently the most important regulator of oxygen homeostasis (11,111). HIF-1 is activated by hypoxia as part of a broad transcriptional cascade. HIF-1 regulates numerous genes that are involved in several processes, including autophagy, angiogenesis, cell division and proliferation. Hypoxia-responsive genes, including *NFκB1* (112), VEGF and HREs, are activated by the HIF-1 activator complex. HIF-1 Aryl hydrocarbon Receptor Nuclear Translocator (HIF-1β/ARNT) and HIF-1α are two protein subunits that are typically present in cells but only activated under hypoxia-level conditions and can form the HIF-1 activator complex. Under normoxic conditions, the HIF-1α subunit is synthesized and destroyed, but it accumulates when exposed to conditions with low or no oxygen. The regulatory roles of HIF include the production of specific chemokines and interleukins, such as TNF, which activate certain transcription factors, such as *NFκB1*. Activated

HIF-1 and *NFκB1* regulate genes involved in vascular reactivity and remodeling, angiogenesis, glucose, energy metabolism, erythropoiesis, iron homeostasis, cell proliferation and survival, causing the disruption or dysfunction in insulin metabolism and glycolysis and regulating the storage of glucose and production of fat NFKB (6,11,94,113). This phenomenon leads to the development of obesity and intolerance of losing weight with diets and sports.

Fig. 1 shows the hypoxia pathway and inflammatory-induced obesity. HIF-1a and NF-kB crosstalk regulate essential inflammatory cytokines in adipose tissue hypoxia. HIF-1α is activated in response to low oxygen levels. In the context of obesity, the activation of HIF-1α in adipose tissue is associated with inflammatory responses and insulin resistance (114). The hypoxic environment in adipose tissue activates various pathways, including HIF-1α and NF-κB, leading to the secretion of pro-inflammatory cytokines. Chronic low-grade inflammation and insulin resistance are hallmarks of obesity-related metabolic disorders (115).

11. Conclusion

The present review highlighted the significance of two genetic (HIF-1 rs11549465 and *NFκB1* rs28362491) variants in inflammation-induced obesity and emphasized the potential association between these mutations and obesity. Results indicated the importance of further research on these variants and the exploration of their associations in diverse populations, races and countries. Researchers should investigate these genetic variants to elucidate their role in obesity. Moreover, further studies should provide a basis for formulation of public health policies aimed at promoting healthy lifestyle choices to mitigate the prevalence of obesity.

The significance of HIF-1 rs11549465 and *NFκB1* rs28362491 variations with obesity through the hypoxia pathway and inflammatory-induced obesity provides a foundation for further research on genetics and inflammatory-induced obesity; the combination of the two pathways increases obesity status.

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Competing interests

The authors declare that they have no competing interests.

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