

The impact of high-fat diet-induced oxidative stress on micro RNA's in various tissues: A review

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Abstract

Stress is the body's reaction to any kind of injury or danger. It is linked to the production of oxidative free radicals, which are responsible for a variety of acute, chronic, and potentially fatal illnesses and diseases. Free radicals, due to their extreme reactivity, can harm or even kill cells. A High-Fat Diet (HFD) causes "oxidative stress", which is characterized by an increase in the body's generation of Reactive Oxygen Species (ROS) as a result of higher levels of triglycerides and Free Fatty Acids (FFA). HFD-induced oxidative stress alters cellular function by affecting transcriptional factors and mitochondrial enzymes (synthesis/inhibition). ROS and FFA damage the receptors of the epithelium, resulting in epithelial damage that impairs cellular function. ROS levels can harm cells by altering the expression of microRNA (miRNA), a sign of RNA damage. MiRNAs are non-coding RNAs found in animals, plants, and some viruses that play a role in the post-transcriptional regulation of gene expression. These three pathways—RNA cleavage, RNA destabilization, and RNA translation into proteins—all play a role in mRNA expression. The miRNA regulates the up- and down-regulation of mRNA expression for cellular function, enzyme synthesis, and receptor modulation. MiRNA regulates cell function by maintaining the balance between cellular ROS levels and cellular damage.

Introduction

According to the World Health Organization (WHO), 39% of women and men aged 18 and up were overweight or obese in 2016. A High Fat/cholesterol Diet (HFD), sedentary lifestyle, and decreased physical activity all contribute to a variety of progressive diseases/disorders associated with fat deposition. In contrast, fat deposition in adipose tissue is caused by an inability to maintain energy balance and, as a result, weight gain. Overeating causes adipocyte and liver bulkiness as a result of triglyceride accumulation, which is linked to increased inflammation, Non-Alcoholic Fatty Liver Disease (NAFLD), hepatic insulin resistance, altered glucose levels/metabolism, fatty acid metabolism, lipoprotein metabolism, and the production of inflammatory mediators (cytokines).^{1,2} Furthermore, the lipolysis activity of reformed adipose tissue influences the migration of free fatty acids into the blood, resulting in ectopic fat accumulations in the liver and muscle.²

Neuronal damage, endothelial damage, cardiac hypertrophy, and erectile dysfunction are all complications of HFD consumption. Oxidative stress and a decline in antioxidant defense cause irreversible damage to macromolecules and redox signaling mechanisms to be disrupted. The activation of cell signaling pathways that protect against oxidative damage, such as Heat Shock Proteins (HSP) and Mitogen-Activated Protein Kinase (MAPK), causes molecular and cellular damage, as well as lipid peroxidation, m-RNA damage, and protein modifications.² HFD causes elevated ROS species and pro-inflammatory mediators associated with oxidative stress via multiple signaling pathways. HFD has been used in experiments to induce certain disorders associated with consuming large amounts of fat through diet. Conditions include hyperlipidemia, metabolic syndrome, obesity, cardiovascular disease, and insulin resistance. HFD used in various studies contains approximately 60% fat, 20% protein, and 20% carbohydrates.

A microRNA is a type of intragenic RNA that is dedicated to a specific transcription factor. RNA polymerase II transcribes and caps polyadenylates, producing primary-miRNA, an extended primary transcript. MiRNAs are single-stranded RNAs (ssRNAs) with 21-25 nucleotides that are formed from hairpin-shaped precursors and have transcripts that are processed after synthesis. Cell proliferation, cell death, fat metabolism, neuronal patterning, hematopoietic differentiation, and immuni-

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ty are all recognized functions. MiRNAs frequently coincide with chromosomal fragile sites and hot spots for chromosomal abnormalities and detect adjacent cancer susceptibilities associated with tumor development. MiRNAs play distinct roles in the regulation and progression of the transcription process in mammals. They are a powerful tool in gene regulation, with the potential to help develop new therapeutic targets. MiRNAs have an evolutionarily

conserved developmental role and a variety of physiological functions in animals, and they mostly have limited complementarity with their target mRNAs. Table 1 summarizes the different types of miRNA and their biological roles.³

The purpose of this review is to highlight the oxidative stress-related effects of HFD on miRNA in various organs and tissues throughout the body (Table 2). Various research works on the complications associated with the HFD, as well as their targets, are discussed.

HFD-induced oxidative stress

Increased FFA levels increase ROS and superoxide anion radicals due to NADH and FADH deoxidation to NAD⁺ and FAD⁴. HFD raises FFA levels in the body, which leads to increased mitochondrial oxidation and the formation of triglycerides (T.G.s) in the liver. T.G.s increase VLDL and transform them to LDL, increasing the formation of oxidized LDL due to a lack of LDL receptors due to ROS-induced receptor damage. By forming foam cells, oxidized lipids block arterial blood vessels. ROS produced by the HFD caused pro-inflammatory mediators to activate NF- κ B, one of the essential transcription factors in inflammation. Furthermore, this HFD either stimulates the production of NF- κ B-dependent pro-inflammatory molecules like Inducible Nitric Oxide Synthase (iNOS),

Tumor Necrosis Factor (TNF-), and Interferon (IFN-), or NF- κ B induces the expression of ROS. Because of the interaction between superoxides and NO, activated iNOS produces an excessive amount of Nitric Oxide (NO), resulting in an increase in Reactive Nitrogen Species (RNS). All of these interconnected events have the potential to cause a variety of risk factors (includ-

ing altered transcriptional processes, mitochondrial respiration, and enzyme/protein synthesis) as well as chronic illnesses.

HFD effects on adipose tissue

Adipose tissue is an endocrine organ that regulates triglyceride storage and release in order to maintain homeostasis.^{4,5}

Adipocytes grow as a result of hyper-

Table 1. miRNAs and their biological function.

miRNA	Biological role
miR-1	Cardiomyocyte differentiation and proliferation
miR-7	Notch signalling
miR-14	Cell death and proliferation
miR-15a, miR-16-1	Downregulation in B-cell chronic lymphocyte leukaemia
miR-16	Au-rich element mediated mRNA instability
miR-17-92	Upregulated in B-cell lymphoma
miR-32	Antiviral defence
miR-143	Adipocyte differentiation
miR-143, miR-145	Downregulated in colonic adenocarcinoma
miR-146	Development and function of the immune system
miR-155	T-cell development and innate immunity
miR-181	Regulation of granulocyte maturation
miR-196	Development of cell
miR-223	Regulation of granulocytic maturation
miR-273	Neuronal cell fate and development timing
miR-372, miR-373	Insulin secretion
miR-375	Insulin secretion
miR-470	Brain morphogenesis

Table 2. High-fat diet-induced oxidative damage to various tissues/organs.

Tissue/Organ	miRNA	Linked protein/Enzyme	HFD induced Oxidative damage	High-fat diet duration	
	Upregulated miRNA	Downregulated miRNA			
Adipose tissue	MiR-143 ¹	MiR-21 ²	PPAR- γ , Adipocyte fatty acid-binding protein (FABP2) TGF- β (Transforming growth factor)	Adipose cell differentiation Lipid and glucose metabolism Adipocyte multiplication	8- 10 Weeks
	miR-17-92, 142-5p, 142-3p, ³	-	PPAR- γ , Protein kinase-b	Cell differentiation Adipogenesis	20 Weeks
	101, 2368, 2454, 196a, 1031, 146-b3	-		Regulates subcutaneous adipose tissue Visceral adipose tissue Physiology of adipose tissue	14 Weeks
	-	miR-16, 204, 133b, 2723	PPAR- γ ,	Pro-apoptotic function Adipogenesis	20 Weeks
Liver Tissue	MiR-122, 467-b	miR-21	Hepatic fatty acid-binding protein (FABP2) Phosphatidylinositol-4, 5-bisphosphate 3-kinase (PI3K) AK (protein kinase).	Regulates hepatic cholesterol levels Lipoprotein lipase activity Fat accumulation in the liver	8- 11 Weeks
		miR-451, miR-16, miR-103/107, miR-669, miR-155, 146	PPAR- γ , Protein kinase-b	Hepatic steatosis ⁴ Fatty acid synthesis ⁵ increased Oxidised LDL	6-12 Weeks
Cardiac Tissue	miR-451	-	Erythroid transcription factor-4 (GATA-4), Calcium-binding protein 39	Altered Cardiac myocyte functioning and morphology ²	20 Weeks
Endothelial Tissue	miR-29b	miR-1	-	Apoptosis of endothelial cells	6 Weeks
Brain Tissue	miR-375	-	Pyruvate dehydrogenase lipoamide kinase isozyme 1 (Pdk1), myocotrophin ⁶	Cell death/Apoptosis	

plasia and hypertrophy. T.G.s are increased and stored in adipocytes, resulting in adipocyte hypertrophy and hyperplasia, which cause adipocyte expansion. HFD causes oxidative stress, which damages miRNAs and targets their importance in enlarging existing adipocytes and adipogenesis or adipocyte differentiation during obesity.⁶ MiR-103 and miR-107 appear to promote Endoplasmic Reticulum (ER) stress-mediated death in pre-adipocytes by specifically targeting the Wnt3a/-catenin/Activating Transcription Factor 6 (ATF6) signaling pathway. As a result, MiR-103 and MiR-107 may be responsible for the increased adipocyte apoptosis in WAT seen in obesity.⁷

HFD research looked into specific changes in miRNA expression (miR-21 and miR-143). Body weight, mesenteric fat, plasma leptin concentration levels, peroxisome proliferator- receptor- (PPAR-) expression, and adipocyte fatty acid-binding protein are all regulated by miR-143 (aP2). The miR-143 targets the extracellular signal-regulating kinase-5 and is involved in adipocyte proliferation, while (PPAR-) regulates adipocyte differentiation and FABP-2 has an impact on lipid and glucose metabolism. Through the modulation of the endogenous Transforming Growth Factor (TGF-) signaling pathway, miR-21 reveals its involvement in adipogenic separation in mesenchyme stem cells of adipose tissue. HFD-induced oxidative stress alters miR-21 expression and increases adipocyte multiplication, leading to obesity.⁸

Other miRNAs affected by oxidative stress include the miR-17-92 band, 101, 2368 (differentiation by regulating PPAR-), miR-2454 (subcutaneous adipose tissue), miR-196a (visceral adipose tissue), miR-142-5p and miR-142-3p (regulates adipogenesis by acting on protein kinase-b), miR-103, miR146-b.⁹

Diet-induced obesity and metabolic disorders in rodents that resemble human metabolic syndrome are associated with an increase in visceral adipose tissue, specifically adipocyte size, and have a significant impact on adipose tissue functionality. White adipose tissue secretes a variety of pro- and anti-inflammatory factors, such as adipokines, leptin, adiponectin, and cytokines like tumor necrosis factor- α (TNF- α) and interleukin-6 (IL-6).

HFD effects on liver tissue

Non-alcoholic fatty liver disease is slowed by a high fat intake (NAFLD). Non-Alcoholic Steatohepatitis (NASH) is a severe form of NAFLD that causes liver damage due to steatosis.¹⁰

NAFLD, non-alcoholic liver damage

that leads to NASH, cirrhosis, and hepatic carcinoma. Various individuals' laboratory reports revealed abnormal changes in hepatic markers, indicating NAFLD. HFD consumption reduces oxidative phosphorylation, a protective mechanism that protects the liver from oxidative stress, and is associated with changes in miRNA expression. HFD-induced oxidative stress in the liver alters the expression of three miRNAs (miR-122, miR-467b, and miR-21) and reduces the mitochondrial enzymes responsible for Oxidative Phosphorylation (OXPHOS) and a specific liver miRNA that controls enzyme synthesis and metabolic process.

MiR-122, miR-467b, and miR-21 are lipid metabolism regulators that regulate enzymes. MiR-122 regulates cholesterol levels in the liver and serum; mir-467 b regulates Lipoprotein Lipase (LPL) levels; and miR-21 regulates FABP7 levels (Fatty Acid-Binding Protein 7). HFD-induced oxidative stress affects OXPHOS by down-regulating miR-467b expression, which is linked to a decrease in phosphatidylinositol-4, 5-bisphosphate 3-kinase (PI3K), and A.K. (protein kinase). MiR-21 inhibition upstreams FABP7 and increases fat accumulation in the liver (NAFLD).¹¹

Several findings on miRNA have been made, including down-stream miR-451 being associated with Non-Alcoholic Steatohepatitis (NASH), miR-16, miR-103/107, and miR-669 downregulation impacting the translation of Fatty Acid Synthase (FASN) and V-Mycavian Myelocytomatosis viral oncogene homolog (MYC), and decreased expression of miR-155 and miR-146 increasing oxidised.

The miRNA linked to liver tissue damage alters the genes involved in receptors such as LDL and VLDL receptors, triglyceride metabolism, cholesterol hydrolysis, and triglyceride lysosomes.

HFD's effects on cardiac tissue

HFD-related oxidative stress alters the morphology of heart tissue and disrupts normal heart function, ultimately leading to cardiac failure (Figure 1). It was recently discovered to increase the profusion of GPR43 into the liver and GPR120 into the heart, thereby selectively facilitating metabolic processes and cardiac function.¹²

HFD increases the expression of miR-451, which controls the transcription factors erythroid transcription factor-4 (GATA-4) and Calcium-binding protein 39 (Cab-39). When combined with Nkx2-5 and Tbx5,

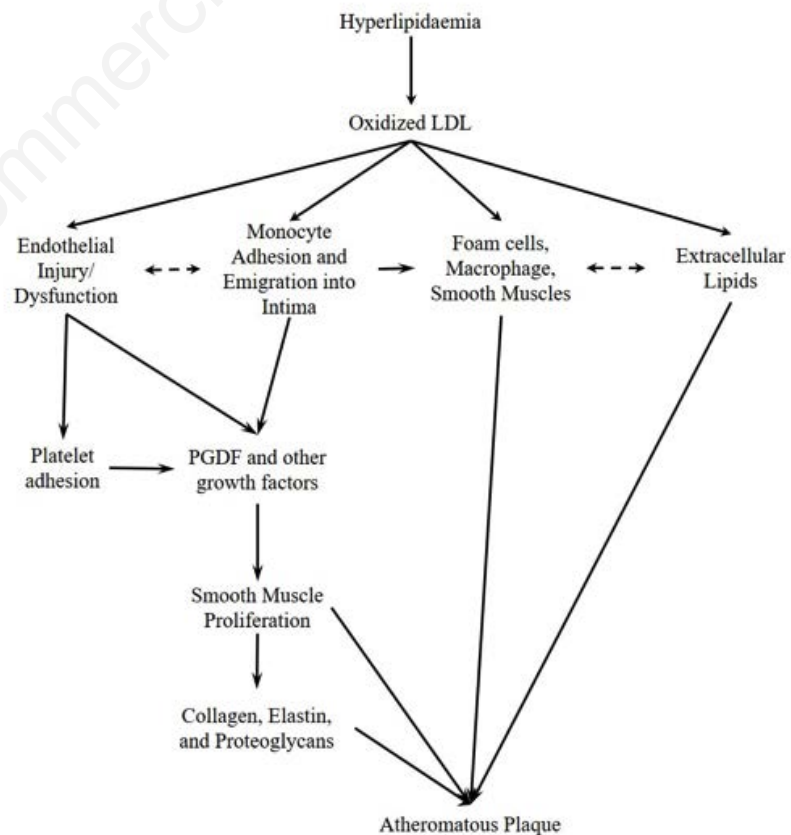


Figure 1. Effect of HFD induced oxidative damage on CVD, Renal damage, and Insulin resistance

GATA-4 promotes hypertrophic growth of cardiac myocytes. GATA-4 regulates cardiac tissue morphology and survival. Cab-39 is a Liver kinase B1 protein (Scaffolding protein) as well as a kinase of 5' AMP-activated Protein Kinase (AMPK) - as a hypertrophy knock model.¹³ HFD's ROS effect results in left ventricular hypertrophy, arterial hypertension, diastolic dysfunction, endothelial dysfunction, coronary microvascular disease, and autonomic dysfunction. Lipid accumulation, altered calcium homeostasis, increased fibrosis and stiffness, abnormal autophagy, mitochondrial dysfunction, and increased oxidative stress result in fatty acid oxidation, mitochondrial dysfunction, and increased NADPH oxidase activity.¹⁴

HFD's effects on endothelial tissue

High-fat diets have been linked to atherosclerosis, a type of cardiovascular disease. Atherosclerosis is characterized by thickening of the endothelium (inner walls) of blood vessels. The accumulation of fatty substances, cholesterol, calcium, and cellular waste causes a blockage of blood flow, resulting in high blood pressure and atherosclerosis.¹² Endothelial dysfunction affects NO bioavailability through decreased endothelial NO synthase expression or activity, as well as increased NO scavenging. Diet and nutrition continue to be important factors in the investigation of atherosclerosis. Endothelial Lipase (EL) levels are elevated in a high-fat diet, which is linked to atherosclerosis and inflammation. Macrophages secrete EL, which is involved in the metabolism of blood lipoproteins. PPAR-gamma, like EL, regulates lipid metabolism and inflammation. EL increases the upregulation of LDL receptors and the binding of LDL, resulting in vessel blockage.¹⁵ The development of atherosclerosis is linked to endothelial cell permeability and apoptosis, and miR-1 downregulation is involved. It increases the expression of Myosin Light Chain Kinase (MLCK) and decreases the phosphorylation of Extracellular signal-Regulated Kinase (ERK). When phosphorylated, these kinases affect permeability and play a role in inflammatory responses. MiR-29b regulates endothelial permeability and the integrity of arterial walls; its involvement in apoptosis is dependent on the level of miR-29b expression.¹⁶

HFD's effects on renal tissue

HFD increases the risk of lipotoxic kidney injury, which leads to chronic kidney injury and, eventually, renal disease associated with CVD and diabetes (Type-II). FFA, ROS production, and mitochondrial dys-

function are all events that occur in renal lipotoxicity. The production of ROS by FFAs and the subsequent increase in mitochondrial membrane permeability depolarizes the mitochondria, causing cell injury in the renal tubules. HFD consumption causes kidney damage by increasing ROS, which could be a mechanism for renal lipotoxicity.¹⁷ MnSOD is a major antioxidant found in mitochondria that protects the Kidney from oxidative stress. HFD increases miRNA expression, which causes p66shc-linked ROS production, which inhibits MnSOD, resulting in oxidative stress and renal damage. P66shc is a transcriptional factor that promotes oxidative stress by suppressing the MnSOD promoter. P66shc migrates to the mitochondrial intermembranous space, binds to, and oxidizes cytochrome c, resulting in excessive ROS production and depolarization of the mitochondria. FFA levels boost the p66shc promoter, which boosts renal expression. Due to an imbalance between kidney lipogenesis and lipolysis caused by HFD consumption, renal injury manifests as lipid accumulation, glomerulosclerosis, interstitial fibrosis, and albuminuria.

HFD effects on pancreatic tissue

It is clear that a high-fat diet raises free fatty acid and ROS levels in the body and contributes to the development of Non-Insulin-Dependent Diabetes Mellitus (NIDDM) by damaging pancreatic tissue and altering miRNA expression. Free fatty acid oxidation reduces glucose uptake by altering the pancreatic enzymes hexokinase-II, glucose-6-phosphate, and pyruvate dehydrogenase. The action of free fatty acids on Mitochondrial Acetyl Co-A and NADH/NAD⁺ ratios of pancreatic mitochondria inhibited these enzymes.¹⁸ HFD also reduces dendritic spine density, LTP at Schaeffer collateral CA1 synapses, and Brain-Derived Neurotrophic Factor (BDNF) levels in the hippocampal region, which is linked to insulin resistance and Alzheimer's Disease (A.D.). The miRNA involved in insulin resistance caused by oxidative damage is not studied in Craft *et al.*'s¹³ research. Human studies have revealed that lipid and free fatty acid infusions affect glucose elimination in patients with hyperglycemia and euglycemic hyperinsulinemia.¹⁸ Similarly, as the primary site for FFA-associated insulin sensitivity, free fatty acid levels influence muscle glycogen synthase.

HFD effects on intestine tissue

Oxidative stress is a risk factor for various cancers, and high-fat diets increase oxidative stress, which is linked to colorec-

tal cancer. Ulcerative colitis and colon metastasis are caused by changes in the miRNA (miR-425-p, miR-100a, miR-194-1-a, miR-378-3p/422b-a, miR-718p, miR-196a, miR-669-a, and miR-155. MiR-196a influences pro-oncogenesis by increasing phosphorylation and, as a result, cell proliferation in response to high-fat feeding. Changes in dietary energy balance modulate the insulin-like growth factor-1 (IGF-1) and mammalian Target Of Rapamycin (mTOR) pathways, emphasizing the link between obesity and cancer.²⁰

MiRNAs such as miR-150-a, miR-351-a, miR-16-2-a, miR-694-p, let7f-1-a, miR-682a, miR-133a*-5p-a, miR-34c-p, miR-138-a, and miR-133a-1-3p-a are also present. MiR-150a suppresses tumor growth by increasing apoptosis and reducing proliferation. Other tumor-suppressing miRNAs, such as miR-34c, let-7, and miR-16, were also suppressed by the high-fat diet. MiRNAs like miR-196, miR-155, and miR-150 promote cancer progression by increasing cell proliferation and decreasing apoptosis.²¹

Several researchers are working on the intestinal carcinogenesis caused by high-fat diet consumption. HFD disrupts the intestinal microbial number and composition, promoting tumor development in cancer-prone individuals' small intestines. The oxidative stress caused by a high fat diet has an impact on digestion, including altered gastric emptying and constipation.

HFD effects on brain tissue

HFD causes central nervous system neurons to die by activating apoptotic pathways and disrupting normal cell proliferation. It harms the enteric nervous system by targeting miR-375 in enteric ganglia and decreasing the levels of regulatory proteins in eukaryotes (14-3-3), pyruvate dehydrogenase lipoamide kinase isozyme 1 (Pdk1), and myocotrophin. HFD reduces superoxide dismutase and catalase activity while increasing thiobarbituric acid reactive substances and glutathione oxidase activity, resulting in oxidative damage in the hippocampus. A study on the effects of a high-fat diet on the Blood-Brain Barrier (BBB), with a focus on the hippocampus, found alterations in glucose transporter 1 (Glut-1; a transporter tangled transport of glucose across the BBB and blood vessels) in Cornus ammonis 1 (CA1), Cornus ammonis 2 (CA2), Cornus ammonis 3 (CA3), Cornus ammonis 4 (CA4). SMI-71 levels were significantly lower in the CA1 region of the hippocampus and parietal cortex of HF fed rats. Tight junction proteins, occluding proteins, and scaffold proteins are examples of BBB proteins. Occludin expression is down

in blood vessels throughout the hippocampus. Occluding was likely observed upstream in neurons of the gyrus and mossy fibers of the CA3 region. A high-fat diet can alter brain vascular constituents, cause miRNA damage that leads to BBB disorder, and change the function of brain endothelial cells. Studies are required to determine the direct mechanisms.²¹

HFD effects on corporal tissue

HFD-associated oxidative damage has an impact on erectile dysfunction because it is linked to obesity and is an early indicator of cardiovascular disease. Nitric Oxide (NO) is a significant mediator of penile erection, and tetrahydrobiopterin (BH4) is a prominent co-factor in NO Synthase (NOS). Increased oxidative stress decreased cellular B.H. levels, HFD induced aortic endothelial dysfunction, and miR-425 negatively controls natriuretic peptide, a potent vasodilator, and regulates smooth muscle tone in the corpus cavernosum. 22 HFD causes oxidative damage to corporal tissue by increasing the expression of miR-720, miR-1937a, miR-1937c, miR-205, and miR-151-5p while decreasing the expression of miR-550, miR-425, miR-134, miR-153, and miR-26b.²²

Conclusions

This review focuses on the tissue damage caused by HFD-induced oxidative stress, which is characterized by increased ROS and free radicals. Oxidative stress is the root cause of many diseases, including heart disease, cancer, lung disease, diabetes, and rheumatoid arthritis. These ROS and free radicals also influence transcription by altering miRNA expression. HFD consumption increases the production of ROS and free radicals, resulting in oxidative stress. HFD causes direct cell and tissue damage by impairing mitochondrial respiration and enzyme synthesis, as well as indirectly affecting miRNA expression, which is responsible for transcriptional processes and protein synthesis.

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