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REVIEW

Multiple Roles of Palmitic Acid in Cardiovascular Diseases

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Abstract: Palmitic acid (PA) is a 16-carbon long-chain saturated fatty acid (SFA) in the human body and a major component of dietary SFAs. PA plays a significant regulatory role in the pathogenesis and progression of various diseases, particularly cardiovascular diseases (CVD). The human body acquires PA through endogenous de novo synthesis and exogenous dietary intake, and its concentration in plasma is relatively stable; however, the concentration of PA can increase several-fold in the plasma of patients with CVD. This review focuses on the biosynthetic pathways of PA and its mechanistic involvement in atherosclerosis (AS), ischemic heart disease (IHD), and ischemic stroke (IS). Elucidating the mechanistic contributions of PA to these disease processes may provide critical insights for developing novel targeted therapies.

Keywords: palmitic acid, molecular mechanisms, atherosclerosis, ischemic heart disease, ischemic stroke

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Introduction

Palmitic acid (PA) is a 16-carbon long-chain saturated fatty acid (SFA),[1,2] which is widely found in animals and plants.[3] It is an essential constituent acid of adipose tissue and the most abundant SFAs in the body,[4] accounting for approximately 44–52% of the body's total fat content[5] and 28–32% of the total serum fatty acid (FA).[6]

Cardiovascular diseases (CVD) is one of the deadliest diseases worldwide.[7] CVD mainly includes coronary heart disease, cerebrovascular disease, peripheral artery disease, rheumatic heart disease, congenital heart disease, deep vein thrombosis, and pulmonary embolism.[8] In addition, atrial fibrillation is very closely linked to atherosclerosis (AS) and has largely the same pathophysiological basis as other CVD: endothelial dysfunction and inflammation, coronary artery disease is an important and clinically relevant risk factor of atrial fibrillation.[9] According to the World Health Organization, 17.3 million people died from CVD in 2016, accounting for 31.5% of all deaths. This number is expected to increase to 23.6 million by 2030.[8] The mortality rate of CVD has exceeded that of cancer, infectious diseases, maternal diseases, and neonatal diseases.[10] Hyperlipidaemia (elevated total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), and reduced high-density lipoprotein cholesterol (HDL-C)), Systemic inflammation, and oxidative stress play a crucial role in the development of CVD.[11–14]

Emerging evidence indicates that elevated circulating FA levels correlate with CVD incidence, and free fatty acids show diagnostic potential as early biomarkers for AS.[15–20] In vivo and in vitro experiments evidence suggests potential mechanisms linking PA intake with CVD pathogenesis.[21,22] Epidemiological studies also indicate that high dietary PA exposure associates with increased CVD risk across diverse populations.[23,24] Elevated serum PA concentrations have been proposed to heighten atrial fibrillation risk primarily through PA's impact on endothelial dysfunction and inflammation.[25] However, critical gaps persist in current research: the analysis of PA's biosynthetic pathways remains

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Table 1 Palmitic Acid Associations with Traditional Cardiovascular Risk Factors

Research Type	Age (Years)	Sex	Conclusion	References
Cross-sectional study	Adult (>18)	Both	No significant associations	[26]
Human multipotent adipose-derived stem (hMADS)	NA	NA	FAs had no effect	[27]
Randomized Controlled Trial (RCT)	Adult (>18)	Both	Palm olein reduced the total, LDL and HDL cholesterol	[28]
Randomized Controlled Trial (RCT)	Adult (>18)	Man	Palm olein has no detrimental effects on plasma lipid	[29]

incomplete, with insufficient mechanistic delineation specific to individual pathologies, particularly AS, ischemic heart disease (IHD), and ischemic stroke (IS); in addition, lack of translational research frameworks connecting PA-related molecular mechanisms to therapeutic strategies; finally, while substantial evidence supports PA's detrimental cardiovascular effects, several studies report context-dependent outcomes (Table 1). To address these gaps, this review: Systematically synthesizes PA's anabolic pathways and pathological mechanisms in AS, IHD, and IS; Identifies novel targetable nodes for CVD prevention/treatment by pinpointing therapeutically exploitable sites within key biological pathways.

Methods

A systematic search was performed across four electronic databases (PubMed, Scopus, Web of Science, and Google Scholar) to comprehensively identify literature examining the association between palmitic acid and specific cardiovascular diseases, namely atherosclerosis, ischemic heart disease, and ischemic stroke. Search results were merged and deduplicated. Initial study inclusion/exclusion was determined by screening titles and abstracts. The review encompassed literature published through December 2024.

The Anabolic Pathways of Palmitic Acid

Endogenous Synthesis and Exogenous Uptake of Palmitic Acid

Palmitic acid is mainly synthesized in the liver. In the de novo synthesis, glucose and glutamine produce pyruvate by glycolysis, which undergoes the tricarboxylic acid cycle in the mitochondria to produce citrate. And then the citrate is cleaved in the cytoplasm by ATP-citrate lyase (ACLY) to Acetyl-CoA and oxaloacetate. Acetyl-CoA is then carboxylated to malonyl-CoA by acetyl-CoA carboxylase (ACC) and condensed by fatty acid synthase (FASN) in a repeated reactions to generate PA.[30,31] The endogenous synthesis of PA is controlled precisely under normal circumstances. However, when carbohydrate intake is excessive, the carbohydrate response element-binding protein (ChREBP) is activated, upregulation of the transcription factor sterol regulatory element binding protein-1c (SREBP-1c) and resulting in insulin production, which subsequently increases PA production[32–34] (Figure 1).

Exogenous Uptake Pathway of Palmitic Acid

Palmitic acid is found in plant oils including palm oil, peanut oil, and coconut oil, as well as in animal fats like butter and cream. Therefore, the human body can also obtain PA through exogenous dietary intake.[35,36] The primary sites for digestion and absorption of fats in the human body are the duodenum and the upper jejunum. When the body consumes fats containing PA from the diet, they are emulsified by bile acids to form hydrophobic fat globules, which are then further broken down into smaller droplets. These droplets are subsequently hydrolyzed by pancreatic lipase into free fatty acids and monoacylglycerol, which are absorbed by the intestinal epithelial cells. In the endoplasmic reticulum (ER) of the epithelial cells, free fatty acids are converted into TG, which then combine with apolipoproteins. These TG, together with apolipoproteins, are transported through chylomicrons to the lymphatic system and eventually enter the bloodstream[37,38] (Figure 1).

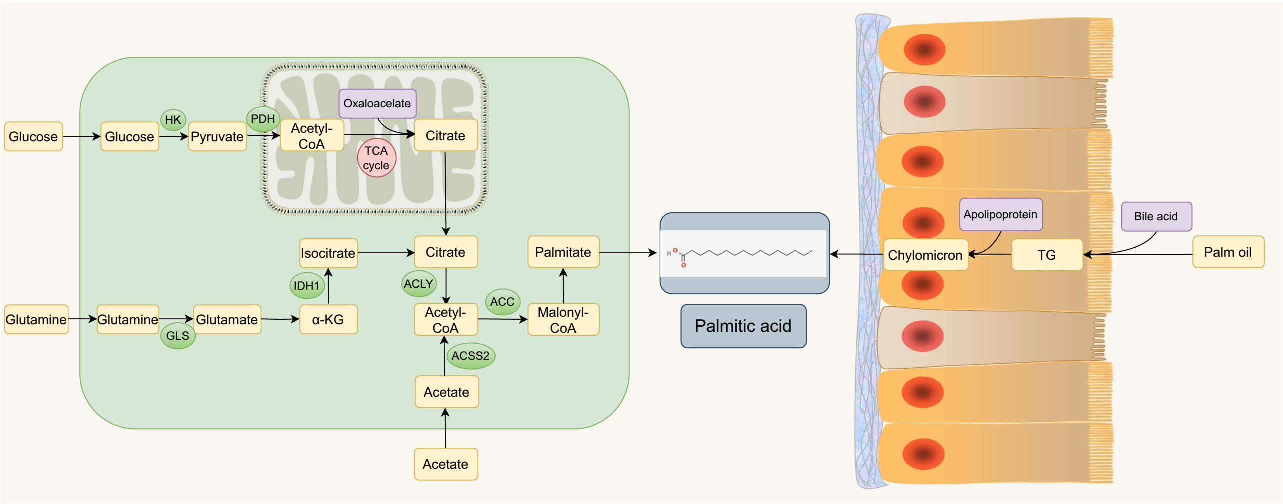

Figure 1 Endogenous synthesis and exogenous uptake of palmitic acid. In the de novo synthesis, glucose and glutamine are enzymatically catalyzed to produce citrate, which is cleaved to acetyl-CoA and oxaloacetate. Acetyl-CoA is carboxylated to malonyl-CoA, which is condensed by the repeated actions of FASN to produce PA. In the process of exogenous uptake, dietary fat is digested into free fatty acids and monoglycerides through the emulsification of bile acids in the duodenum and upper jejunum, which are then absorbed and converted into TG by intestinal epithelial cells, and then combined with apolipoproteins to form chylous particles, which enter the lymphatic system and the ultimately the bloodstream.

Metabolism of Palmitic Acid

The distribution and metabolism of PA in tissues is strictly controlled by the organism, which normally regulates the de novo synthesis pathway according to the amount of exogenous PA consumed.[39,40] First, PA as a kind of FA, have the capability of providing the body with energy through the process of oxidative catabolism.[41,42] PA combines with carnitine to produce an acylcarnitine molecular, and then the acylcarnitine molecular is transported across the mitochondrial membrane to the mitochondrial matrix to generate a molecule of nicotinamide adenine dinucleotide (NADH), a molecule of flavin adenine dinucleotide, reduced ($FADH_2$), and an acetyl-CoA, which is eventually consumed as energy for the body.[43] Secondly, PA is elongated or desaturated for conversion to other FA or compounds,[44] which are produced in the presence of FA elongases (elongation of very long-chain fatty acids 1–7 (ELOVL1-7)) to produce longer chain FA (eg, stearic acid (SA) and arachidonic acid).[45] Moreover, PA synthesized endogenously in adipocytes is converted to other FA or compounds through elongation and desaturation in preference to exogenous PA, thus ensuring that the concentration of PA in tissues is within the normal range to maintain cell membrane fluidity and insulin sensitivity.[46,47] Finally, PA itself can be transformed into an important component of biofilms (phospholipids), which plays an important role in biological processes (eg, cellular proliferation, reproductive processes, and intracellular transport). PA was found to generate phosphatidylcholine and phosphatidylethanolamine (PE) by deacylation in rat hepatocyte, the final synthesis of membrane phospholipids.[48] This process is regulated by membrane-binding transcription factors and can further regulate lipid synthesis.[49]

In obese subjects, the activity of stearoyl coenzyme a desaturase 1 (SCD1) was increased, and SCD1 was associated with insulin sensitivity.[46] However, under pathological conditions including insulin resistance and chronic nutritional imbalance, this regulatory mechanism can be disrupted, leading to excessive PA deposition in the liver and eventually to a series of CVD.[50,51] Several studies have measured plasma PA concentrations in healthy subjects, indicating a range of 100~409 µM. Nevertheless, patients with diabetes, hypertriglyceridemia, and CVD have elevated plasma PA levels (Table 2).

Palmitic Acid and Cardiovascular Diseases

Palmitic Acid and Atherosclerosis

Atherosclerosis is the basis of most CVD and causes of death, for example, coronary heart disease and stroke.[58] It is characterized by the endothelial dysfunction and inflammation, form cells formation from macrophage, atherosclerotic

Table 2 Plasma Palmitic Acid Levels

Study Cohort	Age (Years)	Sex	Plasma PA Level (μmol/L) or (% Total Fatty Acids)	References
Normal subjects	Adult (>18)	Both	122 ± 48	[52]
Normal subjects	Adult (>18)	Both	Man: 409 ± 25 Woman: 349 ± 15	[53]
Normal subjects	Adult (>18)	Both	250	[54]
Normal subjects	Adult (>18)	Both	100	[55]
Diabetic patients			300	
Normal subjects	Adult (>18)	Both	21.35% ±2.66	[56]
Triglyceridemia patients			25.34% ±2.75	
Normal subjects	Adult (>18)	Both	163.9 ± 53.2	[57]
Diabetic patients			234.9 ± 58.1	

plaque formation in the intima of arteries and apoptosis,[59–61] which may result in acute cardiovascular events due to plaque rupture and thrombosis.[62] Studies have demonstrated that the high concentrations of PA in blood are involved in the formation of AS through a variety of biological processes, including hyperlipidaemia,[63,64] inflammation,[65] vascular endothelial damage,[66] form cells formation,[67] and downregulation of apolipoprotein M (APOM).[68]

Palmitic Acid Induces Hyperlipidemia

There is an increased risk of CVD associated with high levels of TC, LDL-C, and lower levels of HDL-C.[69,70] PA can induce AS by altering blood cholesterol levels, particularly through elevating LDL-C levels.[63,64] PA inhibits the expression of low density lipoprotein (LDL) receptors and accelerates the secretion of very low-density lipoprotein (VLDL) from the liver.[51] Genes related to lipid transport, adipogenesis, lipid droplet formation, and glucose and FA metabolism were found to be upregulated after incubation with PA in human hepatocytes cultured in vitro, similar effects were observed in primary cultures of human pancreatic islets.[71,72] Specifically, PA promoted lipid accumulation by upregulating the CCN1/integrin α5β1 pathway.[73] Lipid accumulation and apoptosis were also observed in PA-treated human kidney-2 (HK2).[74] Increased dietary levels of 18:2(n-6) FA lead to lower total and LDL-C levels, while at low dietary levels of 18:2(n-6) FA, increased PA content leads to a significant increase in total and LDL-C levels.[75] Meanwhile, in a controlled metabolic feeding study, PA intake promotes elevated blood cholesterol levels, consistent with previous studies.[76–78] In addition, PA also induces insulin resistance, leading to impaired lipid metabolism. Prolonged exposure of cultured human, rat or mouse islets to PA leads to reduced insulin transcription, impairment of glucose-induced insulin secretion, and finally to β-cell apoptosis.[79–81] PA promotes β-cell apoptosis via mTOR-mediated downregulation of protein kinase B (AKT).[82] In human umbilical cord endothelial cells, PA induces insulin resistance by upregulating human regulator of G protein signaling 2 (RGS2) expression, which inhibit insulin-mediated AKT phosphorylation[83,84] (Figure 2).

Palmitic Acid Mediates Inflammation

Palmitic Acid Promotes the Production of Inflammatory Factors

PA has been shown to directly increase levels of interleukin-6 (IL-6) in vivo and in vitro.[85–87] PA upregulates the expression of C-reactive protein (CRP), tumor necrosis factor-α (TNF-α), and inducible nitric oxide synthase (iNOS) in vascular smooth muscle cells (VSMCs), thereby triggering an inflammatory response in cardiac fibroblasts and inducing apoptosis in VSMCs.[88] PA increases the level of the cysteine-rich angiogenic inducer 61 (CYR61) in endothelial cells, thereby stimulating the production of pro-inflammatory cytokines and pro-apoptotic factors.[89] PA also induces the secretion of interleukin-1β (IL-1β), monocyte chemoattractant protein-1 (MCP-1), and TNF-α by peritoneal macrophages, which activated the inflammatory process in LDLr KO mice and ultimately induced AS formation.[90] In microvascular endothelial cells (EOMA lineage), palmitate stimulates the activation of NACHT, LRR and PYD domains-containing protein 3 (NLRP3) inflammasome.[88] Further studies showed that PA treatment of mouse primary

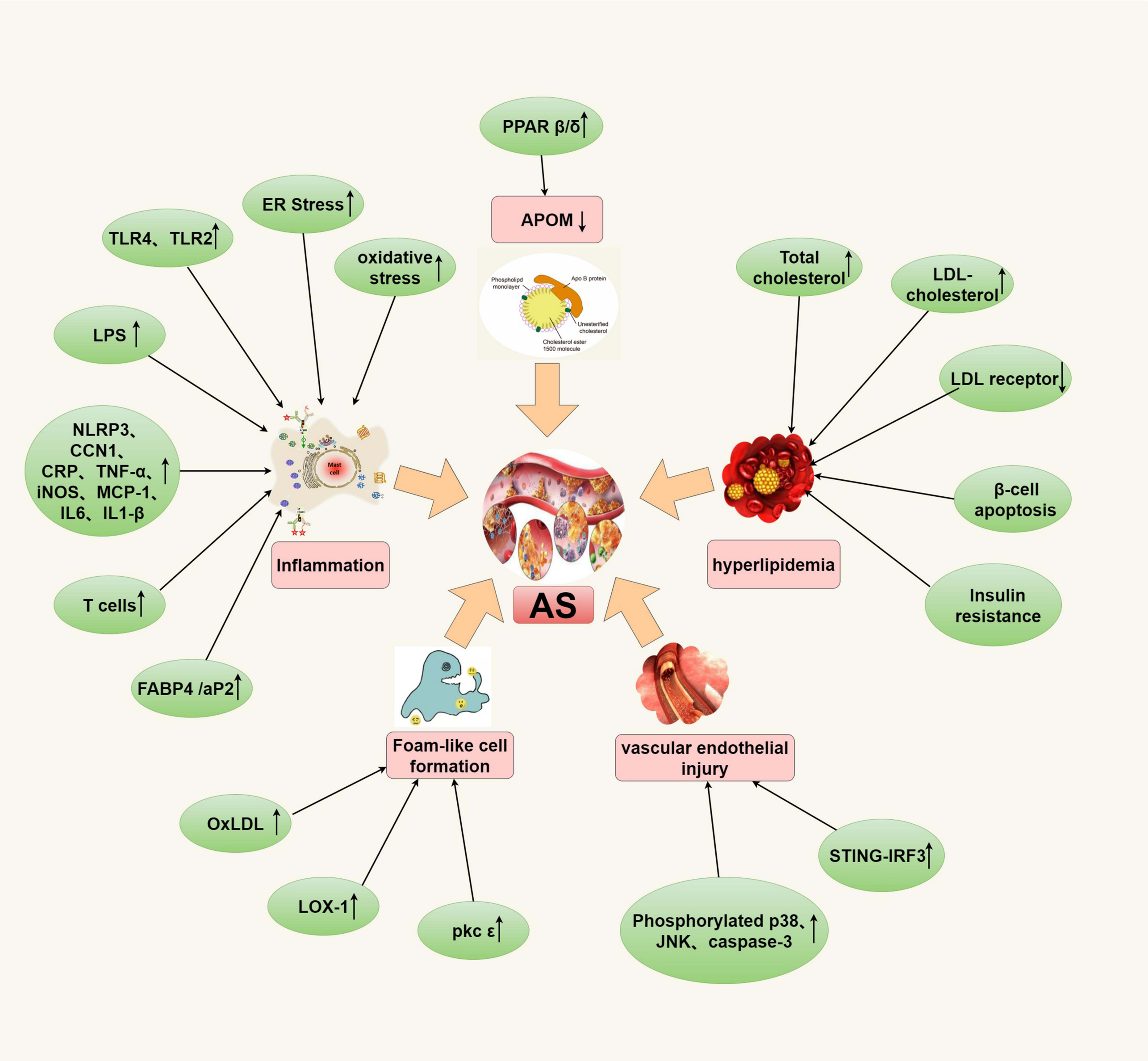

Figure 2 Overview of the mechanisms by which palmitic acid promotes atherosclerosis. PA promotes the progression of by inducing hyperlipidemia, vascular endothelial cell injury, foam cell formation, downregulation of APOM, and proinflammatory effects. Its proinflammatory effect is by activating TLR2 and TLR4, enhanced LPS production and synergistic interactions with LPS, promoting FABP4 expression, amplification of proinflammatory T-cell responses, and induction of ER stress and oxidative stress (↑: increase/activation; ↓: decrease/inhibition).

macrophages induced the formation of crystals within the macrophages, which activated the NLRP3 inflammasome, resulting in lysosomal dysfunction and increased IL-1β release[91] (Figure 2).

Palmitic Acid Activates Toll-Like Receptor 4 (TLR4) to Promote Inflammation

During the inflammatory response, toll-like receptors (TLR) serve as receptors for lipopolysaccharide (LPS).[92–94] Several studies have demonstrated that PA is a TLR agonist that activates TLR4 and TLR2, and induces dimerization among TLR2 and TLR1, TLR2 and TLR6, or TLR4 and TLR6.[95,96] TLR4 translocates into lipid rafts after activation and recruits its downstream adapter molecules (MyD88 and TRIF) to the rafts. After dimerizing with MyD88 or TRIF, initiates pro-inflammatory cytokine and type I interferon production.[84] In addition, activated TLR4 forms a complex with myeloid differentiation protein 2 (MD2), which triggers downstream signaling. However, it is uncertain whether PA is a direct agonist of TLR4-MD2.[97] During the activation of TLR4, atypical protein kinase Czeta (PKCζ) is triggered by

RhoA, next PKCζ activates transforming growth factor β-activated kinase 1 (TAK1), which then participates in the activation of NF-κB,[98] which results in the production of inflammatory cytokines (eg, TNF-α and IL-6).[90] PA promoted the TLR4/phosphorylated-NF-κB signaling pathway by inhibiting Krüppel-like factor 4 (KLF4), upregulated Galectin-3 expression, and improved insulin resistance in macrophage[99] (Figure 2).

Palmitic Acid Activates the Proinflammatory Function of T Cells

T cells are an instrumental component of adaptive immunity and account for 10% of all cells in atherosclerotic plaques.[100,101] Using single-cell sequencing techniques, T cells were found to account for approximately 30–65% of white blood cells in atherosclerotic plaques in humans and mice.[102–104] CD4$^+$ T cells are the predominant T cell subtype in AS and exacerbate atherogenesis in immunodeficient Apoe-/- mice.[105] Researchers found that both CD4$^+$ T cells and CD8$^+$ T cells were increased at atherosclerotic lesion sites associated with acute coronary syndrome.[106] PA activates the proinflammatory function of T cells in four ways: metabolism, activation, proliferation, and polarization.[107] There is evidence that PA increases insulin receptors (IR), insulin-like growth factors 1 (IGF-1), glucose transporter type 4 (GLUT4), and insulin receptor substrate 1 (IRS1) on the surface of T cells, resulting in T cell activation. PA also stimulates the proliferation of T cells and induces the polarization of T cells into proinflammatory subpopulations (Th1 cells and Th17 cells), which then induce an inflammatory response.[107] The addition of 1 mM PA to peripheral blood mononuclear cells activated with anti-CD3 and anti-CD28 increased the proportion of Th1 and Th17 cells, while decreasing that of TH 2 and Treg cells. After in vitro exposure to PA, CD4$^+$ T cells or CD8$^+$ T cells isolated from five healthy, non-diabetic, and glucose-tolerant individuals were found to be activated in a time and concentration-dependent manner[108] (Figure 2).

Palmitic Acid Promotes Inflammation in Synergy with LPS

A high-fat diet increases the levels of short-chain FA by altering the gut microbiome, which leads to elevated levels of LPS and enhanced activation of TLR4.[109] PA also increases ceramide production through de initio synthesis and sphingolipid hydrolysis, thereby enhancing IL-6 expression and TNF-α stimulation induced by LPS.[110] Researchers fed mice both LPS and a high-fat diet rich in PA, which accelerated thoracic aortic atherosclerosis.[111] In human aortic endothelial cells (HAECs) and cardiac microvascular endothelial cells (MICECs), co-treatment with LPS and PA increased IL-6 expression at 36 hours[111] (Figure 2).

Palmitic Acid Promotes the Expression of Fatty Acid-binding Protein 4 (FABP4)

As a cytoplasmic FA carrier protein, FABP4 regulates lipid transport and responses in cells, and is associated with metabolic and inflammatory pathways.[112–115] FABP4 bind a long-chain FA, including PA, SA, oleic acid (OA), linoleic acid (LA), and facilitates the translocation of FAs to specific organelles in the cell (eg mitochondria, peroxisomes, ER, and nucleus), regulates enzymatic activity, and stores excess FAs as lipid droplets.[116] The FABP4 protein has a high affinity for free monounsaturated fatty acids (MUFAs) and polyunsaturated fatty acids (PUFAs) in cells under normal conditions, however, under oxidative stress conditions, the conformation of FABP4 changes, losing its affinity for most FA (except PA), and triggers an inflammatory response.[116] PA increases FABP4 protein expression in macrophages via ER stress.[117,118] The genetic ablation of FABP4 in macrophages showed inhibition of inflammatory signaling, reduced NF-κB pathway activation, and reduced ER stress, protecting mice from AS and dyslipidemia.[119,120] In C2C12 skeletal muscle cells, overexpression of FABP4 protein decreases expression the expression of Sirtuin 3, uncoupling protein 2 (UCP2), and Peroxisome proliferator-activated receptor gamma coactivator 1α (PGC-1α), ultimately leading to increased ROS production in mitochondria and inflammation[121–123] (Figure 2).

Palmitic Acid Activates ER Stress

The ER is involved in the biosynthesis of cholesterol, steroids, and other lipids. A high concentration of free fatty acids (eg PA) may disrupt lipid metabolism, which triggers stress in the ER. When PA is transformed into phospholipids and diacylglycerol (DAG), it accumulates in the ER, causing disruptions in the structure of the ER and activation of the stress sensors.[124–126] The extracellular signal-regulated kinase (ERK) pathway mediates translation of CCAAT/enhancer binding protein (C/EBP) homologous proteins and genes involved in autophagy that are dependent on activating transcription factor 4 (ATF4). Inositol-requiring enzyme 1α (IRE1-α) mediates the expression of tumor necrosis factor receptor-associated factor 2 (TRAF2) and apoptosis signal-regulated kinase 1 (ASK1)/C-jun N-terminal kinase (JNK). They contribute to the ability of stress cells to maintain autophagy, which ultimately triggers ER oxidative and inflammatory signaling pathways leading to apoptosis.[127–131] Phosphorylated ERK, IRE1α, and JNK activation are elevated in both adipose tissue and liver of high fat diet fed mice, which triggers ER stress, eventually leads to apoptosis.[132–135] By upregulating ATF4 and C/EBP homologous protein (CHOP) expression, decreasing cytoplasmic NAD+/NADH, and reducing Sirt1 activity, PA induced ER stress in H9c2 myogblasts.[136] Heart-specific sirt1 knockout mice fed a high palmitate diet were found to express higher levels of CHOP and ATF4.[136] In obese individuals and type 2 diabetes mellitus (T2DM) patients, chronic exposure of β-cells to FA results in ER stress and lipotoxicity[137] (Figure 2).

Palmitic Acid Induces Oxidative Stress

Increased reactive oxygen species (ROS) are the primary cause of palmitate-induced oxidative stress. PA enhances ROS production by promoting lipid uptake in podocytes, and the activity calcium/protein kinase Cα/NADH oxidase 4 (NOX4) pathway in endothelial cells, inhibited mitochondrial respiratory chain complex I and complex III. And the activity of adenine nucleotide carrier protein (ADP/ATP carrier protein).[138–141] Normal mouse hepatocytes AML12 treated with PA. Lipid accumulation, expression of total ROS, mitochondrial ROS, NOX4, inflammasomes, and IL-1β were detected in hepatocytes after 24 h[142] (Figure 2).

Palmitic Acid Induces Vascular Endothelial Injury

Vascular endothelial injury is an important pathological process in the process of AS. Endothelial dysfunction, characterized by impaired vasodilation, inflammation, and thrombosis, triggers future CVD.[143] Reduced endothelial progenitor cells are independent predictors of CVD morbidity and mortality.[144] Lipotoxicity of PA decreases immune surveillance protein DDX58/Rig-1 expression and activity, leading to impaired autophagy and apoptosis;[145] apoptosis in vascular endothelial cells induces endothelial injury and promotes AS progression.[146,147] A member of the angiopoietin-like protein family involved in lipid metabolism promotes endothelial cell proliferation and inhibits PA-induced endothelial cell injury by increasing autophagy, which may inhibit AS.[66] Also, activation of the interferon regulator 3 (IRF3) pathway causes endothelial inflammation.[148] Nitric oxide (NO) from enzymatic NO synthases (NOS) system importantly contributes to vascular homeostasis, in addition to the classical NOS system, NO can also be generated via the nitrate-nitrite-NO pathway.[149] The addition of PA to HAECs resulted in decreased cell viability, reduced intracellular NO production, increased migratory capacity of HAECs, and cellular oxidative stress, ultimately leading to endothelial-to-mesenchymal transition.[150] In endothelial cells, PA upregulated the expression of phosphorylated p38, JNK, and caspase-3, thereby increasing endothelial apoptosis dose- and time-dependently.[151,152] Patients with coronary artery disease showed significantly higher levels of phosphorylation of p38 and mitogen-activated protein kinase (MAPK) in endothelial progenitor cells than healthy individuals.[153] Inhibition or knockout of p38 and MAPK significantly increases the number of circulating endothelial progenitor cells[154] (Figure 2).

Palmitic Acid Promotes Foam Cells Formation

Form cells is one of the major causes of AS, which is due to the accumulation of oxidized LDL (oxLDL) in the arterial intima. Macrophages absorb accumulated oxLDL and form cells. The presence of high levels of PA in the blood enhances the ability of macrophages to take up oxLDL and produce more form cells. OxLDL is a dysfunctional lipid metabolite that is a major promoter of the prothrombotic state in both animal models and human patients.[67,155] In macrophages, PA enhances lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1) expression, promotes oxLDL uptake, a process mediated mainly through the ROS-p38 MAPK pathway.[156] 5-hydroxytryptamine (5-HT) takes part in platelet aggregation, vasoconstriction, proliferation of VSMCs, ER function, and macrophage foam cell formation, play a key role in the development of AS.[157,158] In vitro experiments, exposure of macrophages and human umbilical vein endothelial Cells (HUVECs) to oxLDL or PA demonstrated that activation of 5-HT_{2A} receptor regulates TG synthesis and oxLDL uptake by activating PKCε, resulting in the formation of lipid droplets and even foam cells.[159] PA increases CD146 expression in macrophages, promoting foam cell formation and disrupting migration-related signaling,[160] by activating JNK signaling and inhibiting STAT3 activation, CD146 (Gp130) promotes proinflammatory polarization of M1-like adipose tissue macrophages (ATMs)[161] (Figure 2).

Palmitic Acid Induces Apolipoprotein M Downregulation

Palmitic acid can downregulate the expression of human APOM, promote the accumulation of cholesterol in the blood and induce the development of AS. APOM facilitates HDL metabolism and stabilization, which can reduce blood cholesterol levels, with anti-AS, anti-inflammatory and antioxidant effects.[162] Generally, it is found in hepatocytes and renal tubular epithelial cells, and is weakly expressed in colorectal tissues.[163,164] APOM has been shown to be a possible HDL-carrying receptor for sphingosine 1-phosphate, which enhances HDL-mediated antioxidant effects.[165,166] APOM plays a role in the formation of preb-HDL,[167,168] PA significantly inhibited APOM gene expression in HepG2 cells, and the peroxisome proliferator-activated receptor β/δ (PPAR β/δ) antagonist GSK3787 completely reversed PA-induced downregulation of APOM expression, indicating that PA-induced downregulation of APOM expression is mediated through the PPAR β/δ pathway.[68] A key regulator of lipid metabolism, peroxisome proliferator-activated receptor (PPAR), is expressed in platelets. This receptor upregulates the transcription of lipid metabolizing enzymes, including carnitine palmitoyl coenzyme A transferase-I (GPT-I) and acyl-CoA oxidase, both of which are important to thrombosis and hemostasis[169,170] (Figure 2).

Palmitic Acid and Ischemic Heart Disease

Ischemic heart disease is heart disease caused by narrowing/occlusion of the coronary arteries or by ischemia, hypoxia, or necrosis of the heart muscle due to spasm of the coronary arteries. Approximately 40–80% of the heart's energy comes from FA, several cohort studies have revealed, compared with healthy young subjects, patients with chronic heart failure, myocardial ischemia, T2DM, and obese individuals elevated levels of free fatty acids (include PA) in the blood.[171–177] Additionally, there are studies that indicate that PA levels in adipose tissue are related to IHD incidence. Insull et al found that SA (18:0), lauric acid (12:0), palmitoleic acid (16:1), myristic acid (14:0), and LA (18:2) acids were associated with coronary artery disease, and PA (16:0) content in adipose tissue was associated with plasma cholesterol levels.[178] A study by Lee et al compared the FA composition of adipose tissue in two races with different prevalences of coronary heart disease and found significant differences in PA, palmitoleic, and OA (18:1).[179] Thus, high concentrations of PA, both circulation and adipose tissue, are associated with the incidence of IHD. There was a significant increase in FA uptake and FA oxidation in the heart when the supply of free FA was increased, according to Lopaschuk GD.[180] Replacing saturated FA (FA and SA) with plant-based proteins may reduce the risk of myocardial infarction.[181]

Palmitic Acid Induces Apoptosis in Cardiomyocytes

Palmitic acid induces cardiomyocyte apoptosis by promoting autophagy. Studies have shown that after treating rat cardiomyocytes with PA (0.25 and 0.5 mM) for 18 hours, the number of apoptotic cells and biochemical markers (caspase activation, DNA fragmentation), significantly increased.[182] In cardiomyocytes, PA induces apoptosis by promoting the generation of ceramide and activating the mitochondrial apoptosis pathway, leading to the myofibril disintegration.[183] In a cohort study involving 4249 participants, the correlation between plasma ceramide (Cer) and sphingomyelin (SM) levels and the risk of sudden heart failure was investigated. The results showed that high levels of PA were associated with a higher risk of heart failure during a median follow-up of 9.4 years.[184] Ischemic events are believed to increase the flow of free fatty acids to cardiomyocytes, thereby increasing oxidative stress and causing cardiomyocyte damage.[185–188] When the heart is exposed to excessive energy (eg, glucose, free fatty acids, and TG) and growth factors (eg, insulin and leptin) over a long period, it accelerates the development of cardiomyopathy, leading to cardiac hypertrophy and failure. These processes are driven by oxidative stress induced by glucolipotoxicity and become the main drivers of cell apoptosis[189] (Figure 3).

Palmitic Acid Promotes Cardiomyocyte Ferroptosis

Ferroptosis is an iron-dependent form of programmed cell death.[190] The primary mechanism of ferroptosis is the induction of cell death through the action of divalent iron or lipoxygenases. Additionally, the expression of the antioxidant systems glutathione and glutathione peroxidase 4 (GPX4) is also involved in the process.[191] A large body

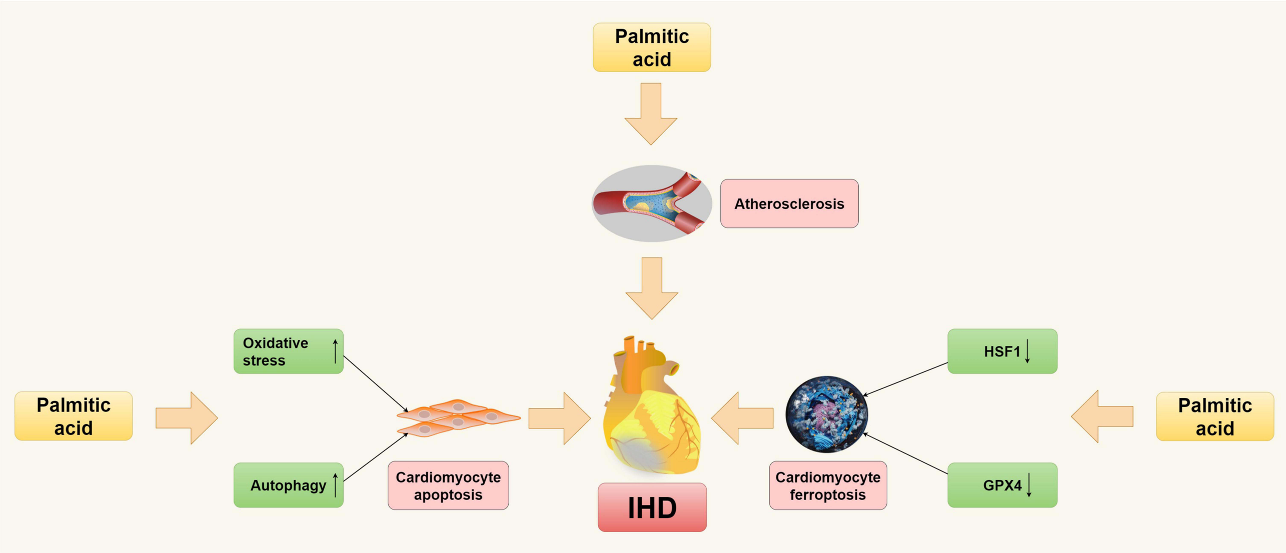

Figure 3 Overview of the mechanism by which palmitic acid promotes ischemic heart disease. PA accelerates progression of induces oxidative stress and autophagic dysregulation, and further triggers cardiomyocyte apoptosis. Additionally, PA promotes cardiomyocyte ferroptosis by reducing the protein expression of Heat Shock Factor 1 and Glutathione Peroxidase 4. These mechanisms collectively drive pathogenesis the onset and development of IHD (↑: increase/activation; ↓: decrease/inhibition).

of evidence has shown that ferroptosis is associated with CVD, particularly with ischemia-reperfusion injury and myocardial infarction.[192] Using different ferroptosis inhibitors significantly reduced PA-induced death in both H9c2s and primary neonatal rat cardiomyocytes. Specifically, PA promotes ferroptosis by reducing the protein expression of heat shock factor 1 (HSF1) and GPX4, while overexpression of HSF1 and GPX4 effectively prevents PA-induced ferroptosis[4] (Figure 3).

Palmitic Acid and Ischemic Stroke

Ischemic stroke has become a major cause of global disease burden due to its high incidence, prevalence, mortality, and disability rates.[193] In 2013, an estimated 6.9 million new IS cases occurred globally, with only 18.25 million surviving in good health, 3.32 million deaths, and 65.54 million disabilities.[194] Plasma levels of docosahexaenoic acid, LA, arachidonic acid, and PA were measured by gas chromatography in 943 participants from the Framingham Heart Study and 1406 participants from three cities of the Bordeaux Study. The results showed that PA is a risk factor for stroke.[195] In a study conducted at the Minneapolis Community Atherosclerosis Risk Center, 3870 white men and women aged 45–64 years (1987–1989) were assessed for plasma cholesterol esters and phospholipid FA, revealing a significant positive correlation between plasma SFAs (particularly PA) and IS.[196]

Palmitic Acid Promotes Neuroinflammation

Palmitic acid can induce chronic inflammation in both peripheral tissues and the central nervous system, for example, hypothalamic neurons.[197–200] In in vitro experiments, PA was found to induce dysfunction in human adipose tissue and soft meningeal artery endothelial cells.[201] Researchers found that when Medin (a common amyloid protein) was combined with PA, there was upregulation of IL-6, IL-8, and PAI-1 gene expression in HUVECs, suggesting combined proinflammatory and prothrombotic effects in IS pathogenesis.[201,202] Mechanistically, PA promotes TLR4 recruitment to lipid rafts in SH-SY5Y neuroblastoma cells, facilitating TLR4/MYD88/TIRAP complex formation a process potentiated by heme-dependent TLR4 activation.[94] PA promoted the upregulation of IL-6 and TNF-α in primary hypothalamic cultures from rats.[203] Further studies confirmed that mice fed a high PA diet showed increased hypothalamic cytokine levels, proinflammatory signaling, neuronal death, and impaired leptin and insulin signaling.[198,204] Direct intraventricular injection of PA also led to hypothalamic inflammation and insulin resistance.[203] PA induces the expression of proinflammatory cytokines in cultured hypothalamic neurons (N42) by increasing ceramide accumulation and lipotoxicity.[92]

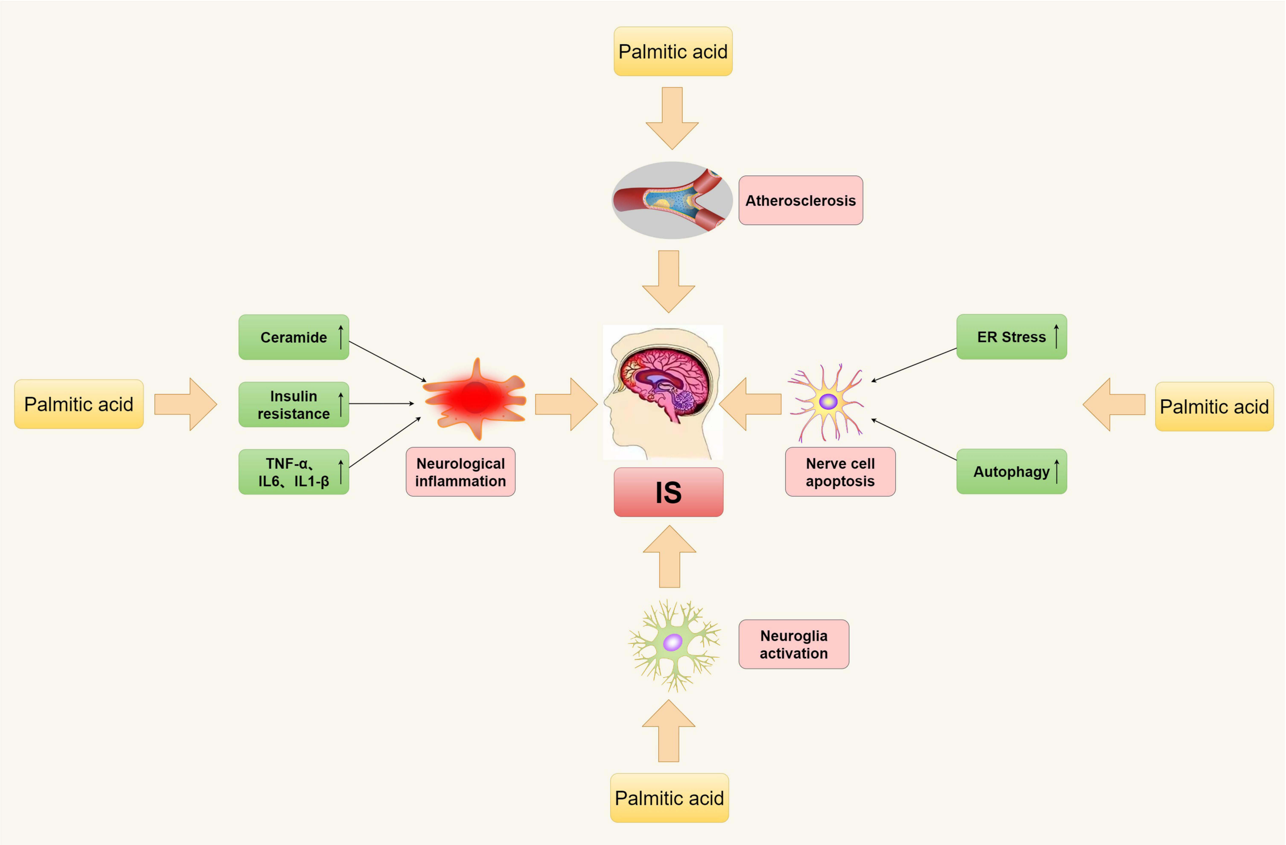

Figure 4 Overview of the mechanism by which palmitic acid promotes ischemic stroke. PA exacerbates IS through multi-target mechanisms: (1) Atherogenesis: Accelerates plaque formation via ceramide overproduction and proinflammatory cytokine induction. (2) Neuroinflammation: Triggers CNS inflammatory cascades through microglial TLR/NLRP3 activation and astrocytic metabolic reprogramming. (3) Neuronal Apoptosis: Induces ER stress-autophagy axis dysregulation in neurons. (4) Glial Activation: Directly stimulates microglial inflammatory signaling and astrocytic lipotoxicity. These interconnected pathways collectively drive neurovascular unit dysfunction, culminating in IS progression (↑: increase/activation).

Additionally, PA interacts with LPS to activate microglial cells, upregulating the expression of proinflammatory cytokines via MAPK, NF-κB, and AP-1 signaling pathways, inducing neuroinflammation in HMC3 cells[205] (Figure 4).

Palmitic Acid Promotes Apoptosis of Neuronal

The lipotoxicity of PA triggers ER stress and autophagic impairment, leading to an increase in apoptosis and the regulation of neuronal plasticity. High concentrations of PA have been shown to induce ER stress in SH-SY5Y cells and mouse brain cells.[206] In SH-SY5Y cells and human glioblastoma cells, PA-induced neurotoxicity and glial cell toxicity, as well as increased oxidative stress in neurons and astrocytes, further promoted cell apoptosis.[207] Mechanistic studies reveal that PA upregulates fatty acid transport protein 1 (FATP1) expression, which enhances prefrontal cortical autophagy dysregulation and ER stress while downregulating neuroplasticity markers including synaptophysin (SYN), brain-derived neurotrophic factor (BDNF), and acetylcholine receptors (AChRs).[208] High-fat diets containing PA activate the MST1/JNK/Caspase-3 signaling pathway in hippocampal HT22 cells, leading to neuronal apoptosis.[209,210] In in vitro experiments, PA significantly increased the autophagic flux in hypothalamic neurons. After PA exposure, the autophagic flux in hypothalamic neurons was suppressed, leading to impaired neuronal autophagy. This autophagic dysfunction was accompanied by changes in lysosomal dynamics, increased Rab7 GTPase activity, ERK phosphorylation, elevated expression of NADPH oxidase 4, and higher levels of inflammation, oxidative stress, and apoptosis in DRG neurons[211] (Figure 4).

Palmitic Acid Activates Glial Cells

Glial cells, primarily composed of microglia and astrocytes, PA can activate glial cells. Microglia are the principal FA sensors in the hypothalamus related to neuronal stress and inflammation and are key mediators of the inflammatory response after stroke and brain injury.[212] PA promotes inflammation by activating TLR receptors distributed in microglia, and also activates NLRP3 inflammasome by increasing TLR4/MyD88/NF-κB p65 signaling, Long-term activation of hypothalamic microglia inhibits neurogenesis in the medial basal hypothalamus (MBH), and the occurrence of IS further activates microglia and exacerbates disease progression.[213,214] Astrocytes are the primary cells responsible for FA oxidation in the brain and play an important role in chronic inflammatory responses associated with obesity and the development of secondary metabolic disorders.[215] Although the brain's energy is primarily provided by glucose PA accumulation in astrocytes activates mitochondrial β-oxidation pathways, generating ATP while inducing proinflammatory activation[216] (Figure 4).

Conclusion and Future Directions

Cardiovascular impact of dietary fatty acids exhibits fundamental dichotomy: Saturated fatty acids, particularly PA, promote cardiovascular pathogenesis through pro-inflammatory, dyslipidemic, and endothelial dysfunction pathways. SA as one of the metabolic products of PA, that exhibits neutral metabolic effects. While monounsaturated (eg, oleic acid) and polyunsaturated fatty acids confer cardioprotection. As the most abundant endogenous and dietary SFA, PA serves as a pathophysiological pivot in atherosclerosis development and cerebrovascular complications. Translation of these mechanistic insights into balanced nutritional interventions represents an actionable strategy for global CVD burden reduction.

However, current limitations must be addressed: current evidence exhibits heterogeneity in PA exposure quantification across studies; different organizations, races, and diseases should adopt specific quantitative standards, rather than simply using the same standard for measurement; moreover, most interventional data derive from preclinical models requiring human validation.

To advance this field, future research should prioritize: establish specific quantitative standards for different organizations, races and diseases; elucidate tissue-specific signaling mechanisms (eg, endothelial vs glial PA sensing); develop targeted therapies disrupting PA-induced inflammatory cascades (eg, RGS2 inhibitors); conduct randomized trials testing precision and personalized nutrition approaches for high-risk populations; establish clinical biomarkers quantifying PA's pathogenic contributions.

Declaration of Generative AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work, the authors used [deep seek] in order to [improve language and readability]. After using this tool, the authors reviewed and edited the content as needed and takes full responsibility for the content of the publication.

Abbreviations

PA, palmitic acid; SFAs, saturated fatty acids; CVD, cardiovascular diseases; AS, atherosclerosis; IHD, ischemic heart disease; IS, ischemic stroke; FA, fatty acid; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; ACLY, ATP-citrate lyase; ACC, acetyl-CoA carboxylase; FASN, fatty acid synthase; ChREBP, carbohydrate response element-binding protein; SREBP-1c, sterol regulatory element binding protein-1c; ER, endoplasmic reticulum; NADH, nicotinamide adenine dinucleotide; $FADH_2$, flavin adenine dinucleotide, reduced; ELOVL1-7, elongation of very long-chain fatty acids 1-7; SA, stearic acid; PE, phosphatidylethanolamine; SCD1, stearoyl coenzyme a desaturase 1; APOM, apolipoprotein M; LDL, low density lipoprotein; VLDL, very low-density lipoprotein; HK2, human kidney-2; AKT, protein kinase B; RGS2, human regulator of G protein signaling 2; IL-6,interleukin-6; CRP, C-reactive protein; TNF-α, tumor necrosis factor-α; Inos, nitric oxide synthase; VSMCs, vascular smooth muscle cells; CYR61, cysteine-rich angiogenic inducer 61; IL-1β, interleukin-1β; MCP-1, monocyte chemoattractant protein-1; NLRP3, NACHT, LRR and PYD domains-containing protein 3; TLR4, Toll-like receptor 4; TLR, toll-like receptors; LPS, lipopolysaccharide; MD2, myeloid differentiation protein 2; pkcζ, atypical protein kinase Czeta; TAK1, transforming growth factor β-activated kinase 1; KLF4, Krüppel-like factor 4; IR, insulin receptors; IGF-1, insulin-like growth factors 1; GLUT4, glucose transporter type 4; IRS1, insulin receptor substrate 1; HAECs, human aortic endothelial cells; MICECs, cardiac microvascular endothelial cells; FABP4, fatty acid-binding protein 4; OA, oleic acid; LA, linoleic acid; MUFAs, monounsaturated fatty acids; PUFAs, polyunsaturated fatty acids; PGC-1α, Peroxisome proliferator-activated receptor gamma coactivator 1α; UCP2, uncoupling protein 2; DAG, diacylglycerol; ERK, extracellular signal-regulated kinase; C/EBP, CCAAT/enhancer binding protein; ATF4, activating transcription factor 4; IRE1-α, inositol-requiring enzyme 1α; TRAF2, tumor necrosis factor receptor-associated factor 2; ASK1, apoptosis signal-regulated kinase 1; JNK, C-jun N-terminal kinase; CHOP, C/EBP homologous protein; T2DM, type 2 diabetes mellitus; ROS, reactive oxygen species; NOX4, calcium/protein kinase Cα/NADH oxidase 4; IRF3, interferon regulator 3; NO, nitric oxide; MAPK, mitogen-activated protein kinase; oxLDL, oxidized LDL; LOX-1, lectin-like oxidized low-density lipoprotein receptor-1; 5-HT, 5-hydroxytryptamine; HUVECs, human umbilical vein endothelial Cells; ATMs, M1-like adipose tissue macrophages; PPAR, eroxisome proliferator-activated receptor; GPT-I, carnitine palmitoyl coenzyme A transferase-I; Cer, ceramide; SM, sphingomyelin; GPX4, glutathione peroxidase 4; HSF1, heat shock factor 1; FATP1, fatty acid transport protein 1; SYN, synaptophysin; BDNF, brain-derived neurotrophic factor, AChRs, acetylcholine receptors; MBH, medial basal hypothalamus.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

1. Ávalos Y, Hernández-Cáceres MP, Lagos P, et al. Palmitic acid control of ciliogenesis modulates insulin signaling in hypothalamic neurons through an autophagy-dependent mechanism. *Cell Death Dis*. 2022;13(7):1–13. doi:10.1038/s41419-022-05109-9
2. Bier DM. Saturated fats and cardiovascular disease: interpretations not as simple as they once were. *Crit Rev Food Sci Nutr*. 2016;56(12):1943–1946. doi:10.1080/10408398.2014.998332
3. Wu KM, Hsu YM, Ying MC, et al. High-density lipoprotein ameliorates palmitic acid-induced lipotoxicity and oxidative dysfunction in H9c2 cardiomyoblast cells via ROS suppression. *Nutr Metab*. 2019;16: 36. doi:10.1186/s12986-019-0356-5
4. Wang N, Ma H, Li J, et al. HSF1 functions as a key defender against palmitic acid-induced ferroptosis in cardiomyocytes. *J Mol Cell Cardiol*. 2021;150:65–76. doi:10.1016/j.yjmcc.2020.10.010
5. Mancini A, Imperlini E, Nigro E, et al. Biological and nutritional properties of palm oil and palmitic acid: effects on health. *Molecules*. 2015;20(9):17339–17361. doi:10.3390/molecules200917339
6. Klein S, Wolfe RR. Carbohydrate restriction regulates the adaptive response to fasting. *Am J Physiol*. 1992;262(5 Pt 1):E631–636. doi:10.1152/ajpendo.1992.262.5.E631
7. Pilz S, März W. Free fatty acids as a cardiovascular risk factor. *Clin Chem Lab Med*. 2008;46(4):429–434. doi:10.1515/cclm.2008.118
8. Benjamin EJ, Muntner P, Alonso A, et al. Heart disease and stroke statistics-2019 update: a report from the American Heart Association. *Circulation*. 2019;139(10):e56–e528. doi:10.1161/cir.0000000000000659
9. Batta A, Hatwal J, Sharma YP. Assessment of coronary artery disease in non-valvular atrial fibrillation: is this light at the end of the tunnel? *Vasc Health Risk Manag*. 2024;20:493–499. doi:10.2147/VHRM.S484638
10. Townsend N, Wilson L, Bhatnagar P, et al. Cardiovascular disease in Europe: epidemiological update 2016. *Eur Heart J*. 2016;37(42):3232–3245. doi:10.1093/eurheartj/ehw334
11. Shramko VS, Polonskaya YV, Kashtanova EV, et al. The short overview on the relevance of fatty acids for human cardiovascular disorders. *Biomolecules*. 2020;10(8):1127. doi:10.3390/biom10081127

12. Gordon T, Kannel WB. Multiple risk functions for predicting coronary heart disease: the concept, accuracy, and application. *Am Heart J*. 1982;103(6):1031–1039. doi:10.1016/0002-8703(82)90567-1
13. Kannel WB, Mcgee DL. Diabetes and glucose tolerance as risk factors for cardiovascular disease: the Framingham study. *Diabetes Care*. 1979;2(2):120–126. doi:10.2337/diacare.2.2.120
14. Gordon T, Castelli WP, Hjortland MC, et al. Diabetes, blood lipids, and the role of obesity in coronary heart disease risk for women. The Framingham study. *Ann Int Med*. 1977;87(4):393–397. doi:10.7326/0003-4819-87-4-393
15. Skeaff CM, Miller J. Dietary fat and coronary heart disease: summary of evidence from prospective cohort and randomised controlled trials. *Ann Nutr Metab*. 2009;55(1–3):173–201. doi:10.1159/000229002
16. Chen X, Liu L, Palacios G, et al. Plasma metabolomics reveals biomarkers of the atherosclerosis. *J Sep Sci*. 2010;33(17–18):2776–2783. doi:10.1002/jssc.201000395
17. Oh PC, Koh KK, Sakuma I, et al. Omega-3 fatty acid therapy dose-dependently and significantly decreased triglycerides and improved flow-mediated dilation, however, did not significantly improve insulin sensitivity in patients with hypertriglyceridemia. *Int J Cardiol*. 2014;176(3):696–702. doi:10.1016/j.ijcard.2014.07.075
18. Hamazaki K, Iso H, Eshak ES, et al. Plasma levels of n-3 fatty acids and risk of coronary heart disease among Japanese: the Japan Public Health Center-based (JPHC) study. *Atherosclerosis*. 2018;272:226–232. doi:10.1016/j.atherosclerosis.2017.12.004
19. Siasos G, Tousoulis D, Oikonomou E, et al. Effects of omega-3 fatty acids on endothelial function, arterial wall properties, inflammatory and fibrinolytic status in smokers: a cross over study. *Int J Cardiol*. 2013;166(2):340–346. doi:10.1016/j.ijcard.2011.10.081
20. Bäck M. Omega-3 fatty acids in atherosclerosis and coronary artery disease. *Future Sci OA*. 2017;3(4):Fso236. doi:10.4155/fsoa-2017-0067
21. Harvey KA, Walker CL, Pavlina TM, et al. Long-chain saturated fatty acids induce pro-inflammatory responses and impact endothelial cell growth. *Clin Nutr*. 2010;29(4):492–500. doi:10.1016/j.clnu.2009.10.008
22. Shen H, Eguchi K, Kono N, et al. Saturated fatty acid palmitate aggravates neointima formation by promoting smooth muscle phenotypic modulation. *Arterioscler Thromb Vasc Biol*. 2013;33(11):2596–2607. doi:10.1161/atvbaha.113.302099
23. Chen Y, Cao Y, Li L, et al. The association between circulating palmitic acid levels and risk of premature coronary artery disease in Chinese patients: a case-control study. *BMC Cardiovasc Disord*. 2025;25(1):412. doi:10.1186/s12872-025-04873-8
24. Jensen PN, Fretts AM, Hoofnagle AN, et al. Plasma ceramides and sphingomyelins in relation to atrial fibrillation risk: the cardiovascular health study. *J Am Heart Assoc*. 2020;9(4):e012853. doi:10.1161/JAHA.119.012853
25. Annevelink CE, Sapp PA, Petersen KS, et al. Diet-derived and diet-related endogenously produced palmitic acid: effects on metabolic regulation and cardiovascular disease risk. *J Clin Lipidol*. 2023;17(5):577–586. doi:10.1016/j.jacl.2023.07.005
26. Gonçalinho GHF, Sampaio GR, Soares-Freitas RAM, Damasceno NRT. Stearic acid, but not palmitic acid, is associated with inflammatory and endothelial dysfunction biomarkers in individuals at cardiovascular risk. *Arq Bras Cardiol*. 2023;120(8):e20220598. doi:10.36660/abc.20220598
27. Caspar-Bauguil S, Kolditz CI, Lefort C, et al. Fatty acids from fat cell lipolysis do not activate an inflammatory response but are stored as triacylglycerols in adipose tissue macrophages. *Diabetologia*. 2015;58(11):2627–2636. doi:10.1007/s00125-015-3719-0
28. Ng TK, Hassan K, Lim JB, Lye MS, Ishak R. Nonhypercholesterolemic effects of a palm-oil diet in Malaysian volunteers. *Am J Clin Nutr*. 1991;53(4 Suppl):1015S–1020S. doi:10.1093/ajcn/53.4.1015S
29. Marzuki A, Arshad F, Razak TA, Jaarin K. Influence of dietary fat on plasma lipid profiles of Malaysian adolescents. *Am J Clin Nutr*. 1991;53(4 Suppl):1010S–1014S. doi:10.1093/ajcn/53.4.1010S
30. Brownsey RW, Boone AN, Elliott JE, et al. Regulation of acetyl-CoA carboxylase. *Biochem Soc Trans*. 2006;34(2):223–227. doi:10.1042/BST0340223
31. Zaidi N, Swinnen JV, Smans K. ATP-citrate lyase: a key player in cancer metabolism. *Cancer Res*. 2012;72(15):3709–3714. doi:10.1158/0008-5472.Can-11-4112
32. Uyeda K, Repa JJ. Carbohydrate response element binding protein, ChREBP, a transcription factor coupling hepatic glucose utilization and lipid synthesis. *Cell Metab*. 2006;4(2):107–110. doi:10.1016/j.cmet.2006.06.008
33. Horton JD, Goldstein JL, Brown MS. SREBPs: activators of the complete program of cholesterol and fatty acid synthesis in the liver. *J Clin Invest*. 2002;109(9):1125–1131. doi:10.1172/JCI0215593
34. Cohen JC, Horton JD, Hobbs HH. Human fatty liver disease: old questions and new insights. *Science*. 2011;332(6037):1519–1523. doi:10.1126/science.1204265
35. Sensoy I. A review on the food digestion in the digestive tract and the used in vitro models. *Curr Res Food Sci*. 2021;4:308–319. doi:10.1016/j.crfs.2021.04.004
36. Lema I, Araújo JR, Rolhion N, et al. Jejunum: the understudied meeting place of dietary lipids and the microbiota. *Biochimie*. 2020;178:124–136. doi:10.1016/j.biochi.2020.09.007
37. Lindquist S, Hernell O. Lipid digestion and absorption in early life: an update. *Curr Opin Clin Nutr Metab Care*. 2010;13(3):314–320. doi:10.1097/MCO.0b013e328337bbf0
38. Chadaideh KS, Carmody RN. Host-microbial interactions in the metabolism of different dietary fats. *Cell Metab*. 2021;33(5):857–872. doi:10.1016/j.cmet.2021.04.011
39. Hulver MW, Berggren JR, Carper MJ, et al. Elevated stearoyl-CoA desaturase-1 expression in skeletal muscle contributes to abnormal fatty acid partitioning in obese humans. *Cell Metab*. 2005;2(4):251–261. doi:10.1016/j.cmet.2005.09.002
40. Peter A, Weigert C, Staiger H, et al. Individual stearoyl-coa desaturase 1 expression modulates endoplasmic reticulum stress and inflammation in human myotubes and is associated with skeletal muscle lipid storage and insulin sensitivity in vivo. *Diabetes*. 2009;58(8):1757–1765. doi:10.2337/db09-0188
41. Fritzen AM, Lundsgaard A-M, Kiens B. Tuning fatty acid oxidation in skeletal muscle with dietary fat and exercise. *Nat Rev Endocrinol*. 2020;16(12):683–696. doi:10.1038/s41574-020-0405-1
42. Smith CD, Lin C-T, Mcmillin SL, et al. Genetically increasing flux through β-oxidation in skeletal muscle increases mitochondrial reductive stress and glucose intolerance. *Am J Physiol Endocrinol Metab*. 2021;320(5):E938–E950. doi:10.1152/ajpendo.00010.2021
43. Koga Y. Thermal adaptation of the archaeal and bacterial lipid membranes. *Archaea*. 2012;2012:789652. doi:10.1155/2012/789652
44. Chen X, Li J, Kang R, et al. Ferroptosis: machinery and regulation. *Autophagy*. 2021;17(9):2054–2081. doi:10.1080/15548627.2020.1810918

45. Igal RA. Stearoyl-CoA desaturase-1: a novel key player in the mechanisms of cell proliferation, programmed cell death and transformation to cancer. *Carcinogenesis*. 2010;31(9):1509–1515. doi:10.1093/carcin/bgq131
46. Collins JM, Neville MJ, Hoppa MB, et al. De novo lipogenesis and stearoyl-CoA desaturase are coordinately regulated in the human adipocyte and protect against palmitate-induced cell injury. *J Biol Chem*. 2010;285(9):6044–6052. doi:10.1074/jbc.M109.053280
47. Dambrova M, Zuurbier CJ, Borutaite V, et al. Energy substrate metabolism and mitochondrial oxidative stress in cardiac ischemia/reperfusion injury. *Free Radic Biol Med*. 2021;165:24–37. doi:10.1016/j.freeradbiomed.2021.01.036
48. Schmid PC, Deli E, Schmid HH. Generation and remodeling of phospholipid molecular species in rat hepatocytes. *Arch Biochem Biophys*. 1995;319(1):168–176. doi:10.1006/abbi.1995.1279
49. Dobrosotskaya IY, Seegmiller AC, Brown MS, et al. Regulation of SREBP processing and membrane lipid production by phospholipids in Drosophila. *Science*. 2002;296(5569):879–883. doi:10.1126/science.1071124
50. Donnelly KL, Smith CI, Schwarzenberg SJ, et al. Sources of fatty acids stored in liver and secreted via lipoproteins in patients with nonalcoholic fatty liver disease. *J Clin Invest*. 2005;115(5):1343–1351. doi:10.1172/jci23621
51. Spady DK, Woollett LA, Dietschy JM. Regulation of plasma LDL-cholesterol levels by dietary cholesterol and fatty acids. *Annu Rev Nutr*. 1993;13:355–381. doi:10.1146/annurev.nu.13.070193.002035
52. Psychogios N, Hau DD, Peng J, et al. The human serum metabolome. *PLoS One*. 2011;6(2):e16957. doi:10.1371/journal.pone.0016957
53. Lopes SM, Trimbo SL, Mascioli EA, et al. Human plasma fatty acid variations and how they are related to dietary intake. *Am J Clin Nutr*. 1991;53(3):628–637. doi:10.1093/ajcn/53.3.628
54. Hoffmann GF, Meier-Augenstein W, Stöckler S, et al. Physiology and pathophysiology of organic acids in cerebrospinal fluid. *J Inherit Metab Dis*. 1993;16(4):648–669. doi:10.1007/bf00711898
55. Trombetta A, Togliatto G, Rosso A, et al. Increase of palmitic acid concentration impairs endothelial progenitor cell and bone marrow-derived progenitor cell bioavailability: role of the STAT5/PPARγ transcriptional complex. *Diabetes*. 2013;62(4):1245–1257. doi:10.2337/db12-0646
56. Paillard F, Catheline D, Duff FL, et al. Plasma palmitoleic acid, a product of stearoyl-coA desaturase activity, is an independent marker of triglyceridemia and abdominal adiposity. *Nutr Metab Cardiovasc Dis*. 2008;18(6):436–440. doi:10.1016/j.numecd.2007.02.017
57. Clore JN, Allred J, White D, et al. The role of plasma fatty acid composition in endogenous glucose production in patients with type 2 diabetes mellitus. *Metabolism*. 2002;51(11):1471–1477. doi:10.1053/meta.2002.35202
58. Zhang J, Wu G, Dai H. The matricellular protein CCN1 regulates TNF-α induced vascular endothelial cell apoptosis. *Cell Biology International*. 2016;40(1):1–6. doi:10.1002/cbin.10469
59. Mozaffarian D. Trans fatty acids - effects on systemic inflammation and endothelial function. *Atheroscler Suppl*. 2006;7(2):29–32. doi:10.1016/j.atherosclerosissup.2006.04.007
60. Libby P. The changing landscape of atherosclerosis. *Nature*. 2021;592(7855):524–533. doi:10.1038/s41586-021-03392-8
61. Galkina E, Ley K. Vascular adhesion molecules in atherosclerosis. *Arterioscler Thromb Vasc Biol*. 2007;27(11):2292–2301. doi:10.1161/atvbaha.107.149179
62. Wu D, Liu J, Pang X, et al. Palmitic acid exerts pro-inflammatory effects on vascular smooth muscle cells by inducing the expression of C-reactive protein, inducible nitric oxide synthase and tumor necrosis factor-α. *Int J Mol Med*. 2014;34(6):1706–1712. doi:10.3892/ijmm.2014.1942
63. Sacks FM, Lichtenstein AH, Wu JHY, et al. Dietary fats and cardiovascular disease: a presidential advisory from the American Heart Association. *Circulation*. 2017;136(3):e1–e23. doi:10.1161/CIR.0000000000000510
64. Astrup A, Magkos F, Bier DM, et al. Saturated fats and health: a reassessment and proposal for food-based recommendations: JACC state-of-the-art review. *J Am Coll Cardiol*. 2020;76(7):844–857. doi:10.1016/j.jacc.2020.05.077
65. Domínguez-López I, Arancibia-Riveros C, Casas R, et al. Changes in plasma total saturated fatty acids and palmitic acid are related to pro-inflammatory molecule IL-6 concentrations after nutritional intervention for one year. *Biomed Pharmacother*. 2022;150:113028. doi:10.1016/j.biopha.2022.113028
66. Zhan W, Tian W, Zhang W, et al. ANGPTL4 attenuates palmitic acid-induced endothelial cell injury by increasing autophagy. *Cell Signal*. 2022;98:110410. doi:10.1016/j.cellsig.2022.110410
67. Shi H, Kokoeva MV, Inouye K, et al. TLR4 links innate immunity and fatty acid-induced insulin resistance. *J Clin Invest*. 2006;116(11):3015–3025. doi:10.1172/jci28898
68. Luo G, Shi Y, Zhang J, et al. Palmitic acid suppresses apolipoprotein M gene expression via the pathway of PPARβ/δ in HepG2 cells. *Biochem Biophys Res Commun*. 2014;445(1):203–207. doi:10.1016/j.bbrc.2014.01.170
69. Bonanome A, Grundy SM. Effect of dietary stearic acid on plasma cholesterol and lipoprotein levels. *New England J Med*. 1988;318(19):1244–1248. doi:10.1056/nejm198805123181905
70. Babayan VK. Plasma cholesterol responsiveness to saturated fatty acids. *Am J Clin Nutr*. 1988;48(6):1520–1522. doi:10.1093/ajcn/48.6.1520
71. Hall E, Volkov P, Dayeh T, et al. Effects of palmitate on genome-wide mRNA expression and DNA methylation patterns in human pancreatic islets. *BMC Med*. 2014;12:103. doi:10.1186/1741-7015-12-103
72. Breher-Esch S, Sahini N, Trincone A, et al. Genomics of lipid-laden human hepatocyte cultures enables drug target screening for the treatment of non-alcoholic fatty liver disease. *BMC Medical Genomics*. 2018;11(1):111. doi:10.1186/s12920-018-0438-7
73. Yao Q, Liu J, Cui Q, et al. CCN1/Integrin α(5)β(1) instigates free fatty acid-induced hepatocyte lipid accumulation and pyroptosis through NLRP3 inflammasome activation. *Nutrients*. 2022;14(18). doi:10.3390/nu14183871
74. Ding XQ, Jian TY, Gai YN, et al. Chicoric acid attenuated renal tubular injury in HFD-induced chronic kidney disease mice through the promotion of mitophagy via the Nrf2/PINK/parkin pathway. *J Agric Food Chem*. 2022;70(9):2923–2935. doi:10.1021/acs.jafc.1c07795
75. Cook S, Konrad S, Goh Y, et al. Palmitic acid does not increase lipoprotein cholesterol levels when the diet contains recommended levels of linoleic acid. In: Proceedings of the Essential Fatty Acids and Eicosanoids Proceedings from the Fourth International Congress on Essential Fatty Acids and Eicosanoids. Edinburgh, Scotland: AOCS Press; 1997.
76. Tholstrup T, Marckmann P, Jespersen J, et al. Fat high in stearic acid favorably affects blood lipids and factor VII coagulant activity in comparison with fats high in palmitic acid or high in myristic and lauric acids. *Am J Clin Nutr*. 1994;59(2):371–377. doi:10.1093/ajcn/59.2.371
77. Hegsted DM, Mcgandy RB, Myers ML, et al. Quantitative effects of dietary fat on serum cholesterol in man. *Am J Clin Nutr*. 1965;17(5):281–295. doi:10.1093/ajcn/17.5.281

78. Keys A, Anderson JT, Grande F. Prediction of serum-cholesterol responses of man to changes in fats in the diet. *Lancet*. 1957;273(7003):959–966. doi:10.1016/s0140-6736(57)91998-0
79. Collins SC, Salehi A, Eliasson L, et al. Long-term exposure of mouse pancreatic islets to oleate or palmitate results in reduced glucose-induced somatostatin and oversecretion of glucagon. *Diabetologia*. 2008;51(9):1689–1693. doi:10.1007/s00125-008-1082-0
80. Moullé VS, Vivot K, Tremblay C, et al. Glucose and fatty acids synergistically and reversibly promote beta cell proliferation in rats. *Diabetologia*. 2017;60(5):879–888. doi:10.1007/s00125-016-4197-8
81. Poitout V, Amyot J, Semache M, et al. Glucolipotoxicity of the pancreatic beta cell. *Biochimica et Biophysica Acta*. 2010;1801(3):289–298. doi:10.1016/j.bbalip.2009.08.006
82. Aggarwal R, Peng Z, Zeng N, et al. Chronic exposure to palmitic acid down-regulates AKT in beta-cells through activation of mTOR. *Am J Pathol*. 2022;192(1):130–145. doi:10.1016/j.ajpath.2021.09.008
83. Gustavo Vazquez-Jimenez J, Chavez-Reyes J, Romero-Garcia T, et al. Palmitic acid but not palmitoleic acid induces insulin resistance in a human endothelial cell line by decreasing SERCA pump expression. *Cell Signal*. 2016;28(1):53–59. doi:10.1016/j.cellsig.2015.10.001
84. Vazquez-Jimenez JG, Corpus-Navarro MS, Rodriguez-Chavez JM, et al. The increased expression of regulator of G-Protein Signaling 2 (RGS2) inhibits insulin-induced Akt phosphorylation and is associated with uncontrolled glycemia in patients with type 2 diabetes. *Metabolites*. 2021;11(2). doi:10.3390/metabo11020091
85. Zhou BR, Zhang JA, Zhang Q, et al. Palmitic acid induces production of proinflammatory cytokines interleukin-6, interleukin-1β, and tumor necrosis factor-α via a NF-κB-dependent mechanism in HaCaT keratinocytes. *Mediators Inflamm*. 2013;2013:530429. doi:10.1155/2013/530429
86. Shirasuna K, Takano H, Seno K, et al. Palmitic acid induces interleukin-1β secretion via NLRP3 inflammasomes and inflammatory responses through ROS production in human placental cells. *J Reprod Immunol*. 2016;116:104–112. doi:10.1016/j.jri.2016.06.001
87. Bunn RC, Cockrell GE, Ou Y, et al. Palmitate and insulin synergistically induce IL-6 expression in human monocytes. *Cardiovasc Diabetol*. 2010;9:73. doi:10.1186/1475-2840-9-73
88. Balta I, Stef L, Pet I, et al. Essential fatty acids as biomedicines in cardiac health. *Biomedicines*. 2021;9(10). doi:10.3390/biomedicines9101466
89. Gan YR, Wei L, Wang YZ, et al. Dickkopf-1/cysteine-rich angiogenic inducer 61 axis mediates palmitic acid-induced inflammation and apoptosis of vascular endothelial cells. *Mol Med Rep*. 2021;23(2). doi:10.3892/mmr.2020.11761
90. Afonso MS, Lavrador MS, Koike MK, et al. Dietary interesterified fat enriched with palmitic acid induces atherosclerosis by impairing macrophage cholesterol efflux and eliciting inflammation. *J Nutr Biochem*. 2016;32:91–100. doi:10.1016/j.jnutbio.2016.01.005
91. Karasawa T, Kawashima A, Usui-Kawanishi F, et al. Saturated fatty acids undergo intracellular crystallization and activate the NLRP3 inflammasome in macrophages. *Arterioscler Thromb Vasc Biol*. 2018;38(4):744–756. doi:10.1161/atvbaha.117.310581
92. Sergi D, Morris AC, Kahn DE, et al. Palmitic acid triggers inflammatory responses in N42 cultured hypothalamic cells partially via ceramide synthesis but not via TLR4. *Nutr Neurosci*. 2020;23(4):321–334. doi:10.1080/1028415x.2018.1501533
93. Hu X, Fatima S, Chen M, et al. Toll-like receptor 4 is a master regulator for colorectal cancer growth under high-fat diet by programming cancer metabolism. *Cell Death Dis*. 2021;12(8):791. doi:10.1038/s41419-021-04076-x
94. Amine H, Benomar Y, Taouis M. Palmitic acid promotes resistin-induced insulin resistance and inflammation in SH-SY5Y human neuroblastoma. *Sci Rep*. 2021;11(1):5427. doi:10.1038/s41598-021-85018-7
95. Huang S, Rutkowsky JM, Snodgrass RG, et al. Saturated fatty acids activate TLR-mediated proinflammatory signaling pathways. *J Lipid Res*. 2012;53(9):2002–2013. doi:10.1194/jlr.D029546
96. Wang Z, Liu D, Wang F, et al. Saturated fatty acids activate microglia via toll-like receptor 4/NF-κB signalling. *Br J Nutr*. 2012;107(2):229–241. doi:10.1017/s0007114511002868
97. Lancaster GI, Langley KG, Berglund NA, et al. Evidence that TLR4 is not a receptor for saturated fatty acids but mediates lipid-induced inflammation by reprogramming macrophage metabolism. *Cell Metab*. 2018;27(5):1096–1110.e1095. doi:10.1016/j.cmet.2018.03.014
98. Teusch N, Lombardo E, Eddleston J, et al. The low molecular weight GTPase RhoA and atypical protein kinase Czeta are required for TLR2-mediated gene transcription. *J Immunol*. 2004;173(1):507–514. doi:10.4049/jimmunol.173.1.507
99. Li J, Mao YS, Chen F, et al. Palmitic acid up regulates Gal-3 and induces insulin resistance in macrophages by mediating the balance between KLF4 and NF-κB. *Exp Ther Med*. 2021;22(3):1028. doi:10.3892/etm.2021.10460
100. Hansson GK, Holm J, Jonasson L. Detection of activated T lymphocytes in the human atherosclerotic plaque. *Am J Pathol*. 1989;135(1):169–175.
101. Jonasson L, Holm J, Skalli O, et al. Regional accumulations of T cells, macrophages, and smooth muscle cells in the human atherosclerotic plaque. *Arteriosclerosis*. 1986;6(2):131–138. doi:10.1161/01.atv.6.2.131
102. Fernandez DM, Rahman AH, Fernandez NF, et al. Single-cell immune landscape of human atherosclerotic plaques. *Nat Med*. 2019;25(10):1576–1588. doi:10.1038/s41591-019-0590-4
103. Depuydt MAC, Prange KHM, Slenders L, et al. Microanatomy of the human atherosclerotic plaque by single-cell transcriptomics. *Circ Res*. 2020;127(11):1437–1455. doi:10.1161/circresaha.120.316770
104. Zernecke A, Winkels H, Cochain C, et al. Meta-analysis of leukocyte diversity in atherosclerotic mouse aortas. *Circ Res*. 2020;127(3):402–426. doi:10.1161/circresaha.120.316903
105. Zhou X, Nicoletti A, Elhage R, et al. Transfer of CD4(+) T cells aggravates atherosclerosis in immunodeficient apolipoprotein E knockout mice. *Circulation*. 2000;102(24):2919–2922. doi:10.1161/01.cir.102.24.2919
106. Winkels H, Ehinger E, Vassallo M, et al. Atlas of the immune cell repertoire in mouse atherosclerosis defined by single-cell RNA-sequencing and mass cytometry. *Circ Res*. 2018;122(12):1675–1688. doi:10.1161/circresaha.117.312513
107. Reilly NA, Lutgens E, Kuiper J, et al. Effects of fatty acids on T cell function: role in atherosclerosis. *Nat Rev Cardiol*. 2021;18(12):824–837. doi:10.1038/s41569-021-00582-9
108. Wang L, Folsom AR, Eckfeldt JH. Plasma fatty acid composition and incidence of coronary heart disease in middle aged adults: the Atherosclerosis Risk in Communities (ARIC) Study. *Nutr Metab Cardiovasc Dis*. 2003;13(5):256–266. doi:10.1016/s0939-4753(03)80029-7
109. Cani PD, Amar J, Iglesias MA, et al. Metabolic endotoxemia initiates obesity and insulin resistance. *Diabetes*. 2007;56(7):1761–1772. doi:10.2337/db06-1491

110. Lu Z, Li Y, Jin J, et al. Palmitic acid enhances the stimulatory effect of lipopolysaccharide on interleukin 6 expression in cardiac microvascular endothelial cells by increasing ceramide production via both de novo synthesis and sphingomyelin hydrolysis. *Am Heart Assoc*. 2013;2013:1.
111. Lu Z, Li Y, Brinson CW, et al. Cooperative stimulation of atherogenesis by lipopolysaccharide and palmitic acid-rich high fat diet in low-density lipoprotein receptor-deficient mice. *Atherosclerosis*. 2017;265:231–241. doi:10.1016/j.atherosclerosis.2017.09.008
112. Furuhashi M, Ishimura S, Ota H, et al. Lipid chaperones and metabolic inflammation. *Int J Inflam*. 2011;2011:1.
113. Furuhashi M, Hotamisligil GS. Fatty acid-binding proteins: role in metabolic diseases and potential as drug targets. *Nat Rev Drug Discov*. 2008;7(6):489–503. doi:10.1038/nrd2589
114. Furuhashi M, Saitoh S, Shimamoto K, et al. Fatty Acid-Binding Protein 4 (FABP4): pathophysiological insights and potent clinical biomarker of metabolic and cardiovascular diseases. *Clin Med Insights Cardiol*. 2014;8(Suppl 3):23–33. doi:10.4137/cmc.S17067
115. Hotamisligil GS, Bernlohr DA. Metabolic functions of FABPs--mechanisms and therapeutic implications. *Nat Rev Endocrinol*. 2015;11(10):592–605. doi:10.1038/nrendo.2015.122
116. Furuhashi M. Fatty acid-binding protein 4 in cardiovascular and metabolic diseases. *J Atheroscler Thromb*. 2019;26(3):216–232. doi:10.5551/jat.48710
117. Erbay E, Babaev VR, Mayers JR, et al. Reducing endoplasmic reticulum stress through a macrophage lipid chaperone alleviates atherosclerosis. *Nat Med*. 2009;15(12):1383–1391. doi:10.1038/nm.2067
118. Li H, Xiao Y, Tang L, et al. Adipocyte fatty acid-binding protein promotes palmitate-induced mitochondrial dysfunction and apoptosis in macrophages. *Front Immunol*. 2018;9:81. doi:10.3389/fimmu.2018.00081
119. Chmurzyńska A. The multigene family of fatty acid-binding proteins (FABPs): function, structure and polymorphism. *J Appl Genet*. 2006;47(1):39–48. doi:10.1007/bf03194597
120. Makowski L, Brittingham KC, Reynolds JM, et al. The fatty acid-binding protein, aP2, coordinates macrophage cholesterol trafficking and inflammatory activity. Macrophage expression of aP2 impacts peroxisome proliferator-activated receptor gamma and IkappaB kinase activities. *J Biol Chem*. 2005;280(13):12888–12895. doi:10.1074/jbc.M413788200
121. Xu H, Hertzel AV, Steen KA, et al. Loss of fatty acid binding protein 4/aP2 reduces macrophage inflammation through activation of SIRT3. *Mol Endocrinol*. 2016;30(3):325–334. doi:10.1210/me.2015-1301
122. Gan L, Liu Z, Cao W, et al. FABP4 reversed the regulation of leptin on mitochondrial fatty acid oxidation in mice adipocytes. *Sci Rep*. 2015;5:13588. doi:10.1038/srep13588
123. Xu H, Hertzel AV, Steen KA, et al. Uncoupling lipid metabolism from inflammation through fatty acid binding protein-dependent expression of UCP2. *Mol Cell Biol*. 2015;35(6):1055–1065. doi:10.1128/mcb.01122-14
124. Kim SK, Oh E, Yun M, et al. Palmitate induces cisternal ER expansion via the activation of XBP-1/CCTα-mediated phospholipid accumulation in RAW 264.7 cells. *Lipids Health Dis*. 2015;14(1):1–12. doi:10.1186/s12944-015-0077-3
125. Akoumi A, Haffar T, Mousterji M, et al. Palmitate mediated diacylglycerol accumulation causes endoplasmic reticulum stress, Plin2 degradation, and cell death in H9C2 cardiomyoblasts. *Exp Cell Res*. 2017;354(2):85–94. doi:10.1016/j.yexcr.2017.03.032
126. Borradaile NM, Han X, Harp JD, et al. Disruption of endoplasmic reticulum structure and integrity in lipotoxic cell death. *J Lipid Res*. 2006;47(12):2726–2737. doi:10.1194/jlr.M600299-JLR200
127. Kim SK, Oh E, Yun M, et al. Palmitate induces cisternal ER expansion via the activation of XBP-1/CCTα-mediated phospholipid accumulation in RAW 264.7 cells. *Lipids Health Dis*. 2015;14:73. doi:10.1186/s12944-015-0077-3
128. Kim DH, Cho YM, Lee KH, et al. Oleate protects macrophages from palmitate-induced apoptosis through the downregulation of CD36 expression. *Biochem Biophys Res Commun*. 2017;488(3):477–482. doi:10.1016/j.bbrc.2017.05.066
129. Go DH, Lee YG, Lee DH, et al. 3-Decylcatechol induces autophagy-mediated cell death through the IRE1α/JNK/p62 in hepatocellular carcinoma cells. *Oncotarget*. 2017;8(35):58790–58800. doi:10.18632/oncotarget.17732
130. Zezina E, Snodgrass RG, Schreiber Y, et al. Mitochondrial fragmentation in human macrophages attenuates palmitate-induced inflammatory responses. *Biochim Biophys Acta Mol Cell Biol Lipids*. 2018;1863(4):433–446. doi:10.1016/j.bbalip.2018.01.009
131. Pardo V, González-Rodríguez Á, Muntané J, et al. Role of hepatocyte S6K1 in palmitic acid-induced endoplasmic reticulum stress, lipotoxicity, insulin resistance and in oleic acid-induced protection. *Food Chem Toxicol*. 2015;80:298–309. doi:10.1016/j.fct.2015.03.029
132. Ozcan U, Cao Q, Yilmaz E, et al. Endoplasmic reticulum stress links obesity, insulin action, and type 2 diabetes. *Science*. 2004;306(5695):457–461. doi:10.1126/science.1103160
133. Ozcan L, Ergin AS, Lu A, et al. Endoplasmic reticulum stress plays a central role in development of leptin resistance. *Cell Metab*. 2009;9(1):35–51. doi:10.1016/j.cmet.2008.12.004
134. Biden TJ, Boslem E, Chu KY, et al. Lipotoxic endoplasmic reticulum stress, β cell failure, and type 2 diabetes mellitus. *Trends Endocrinol Metab*. 2014;25(8):389–398. doi:10.1016/j.tem.2014.02.003
135. Rashid HO, Yadav RK, Kim HR, et al. ER stress: autophagy induction, inhibition and selection. *Autophagy*. 2015;11(11):1956–1977. doi:10.1080/15548627.2015.1091141
136. Yang HY, Chen JY, Huo YN, et al. The role of sirtuin 1 in palmitic acid-induced endoplasmic reticulum stress in cardiac myoblasts. *Life*. 2022;12(2):182. doi:10.3390/life12020182
137. Han J, Kaufman RJ. The role of ER stress in lipid metabolism and lipotoxicity. *J Lipid Res*. 2016;57(8):1329–1338. doi:10.1194/jlr.R067595
138. Chen P, Liu H, Xiang H, et al. Palmitic acid-induced autophagy increases reactive oxygen species via the Ca(2+)/PKCα/NOX4 pathway and impairs endothelial function in human umbilical vein endothelial cells. *Exp Ther Med*. 2019;17(4):2425–2432. doi:10.3892/etm.2019.7269
139. Hua W, Huang HZ, Tan LT, et al. CD36 mediated fatty acid-induced podocyte apoptosis via oxidative stress. *PLoS One*. 2015;10(5):e0127507. doi:10.1371/journal.pone.0127507
140. Jiang XS, Chen XM, Hua W, et al. PINK1/Parkin mediated mitophagy ameliorates palmitic acid-induced apoptosis through reducing mitochondrial ROS production in podocytes. *Biochem Biophys Res Commun*. 2020;525(4):954–961. doi:10.1016/j.bbrc.2020.02.170
141. Rosa Neto JC, Calder PC, Curi R, et al. The immunometabolic roles of various fatty acids in macrophages and lymphocytes. *Int J Mol Sci*. 2021;22(16). doi:10.3390/ijms22168460
142. Xu W, Guo YB, Li X, et al. [Palmitic acid induces hepatocellular oxidative stress and activation of inflammasomes]. *Nan Fang Yi Ke Da Xue Xue Bao*. 2016;36(5):655–659. Sesotho

143. Prabhahar A, Batta A, Hatwal J, et al. Endothelial dysfunction in the kidney transplant population: current evidence and management strategies. *World J Transplant*. 2025;15(1):97458. doi:10.5500/wjt.v15.i1.97458
144. Schmidt-Lucke C, Rössig L, Fichtlscherer S, et al. Reduced number of circulating endothelial progenitor cells predicts future cardiovascular events: proof of concept for the clinical importance of endogenous vascular repair. *Circulation*. 2005;111(22):2981–2987. doi:10.1161/circulationaha.104.504340
145. Frietze KK, Brown AM, Das D, et al. Lipotoxicity reduces DDX58/Rig-1 expression and activity leading to impaired autophagy and cell death. *Autophagy*. 2022;18(1):142–160. doi:10.1080/15548627.2021.1920818
146. Stentz FB, Kitabchi AE. Palmitic acid-induced activation of human T-lymphocytes and aortic endothelial cells with production of insulin receptors, reactive oxygen species, cytokines, and lipid peroxidation. *Biochem Biophys Res Commun*. 2006;346(3):721–726. doi:10.1016/j.bbrc.2006.05.159
147. Moers A, Schrezenmeir J. Palmitic acid but not stearic acid inhibits NO-production in endothelial cells. *Exp Clin Endocrinol Diabetes*. 1997;105(Suppl 2):78–80. doi:10.1055/s-0029-1211804
148. Mao Y, Luo W, Zhang L, et al. STING-IRF3 triggers endothelial inflammation in response to free fatty acid-induced mitochondrial damage in diet-induced obesity. *Arterioscler Thromb Vasc Biol*. 2017;37(5):920–929. doi:10.1161/atvbaha.117.309017
149. Carlström M, Weitzberg E, Lundberg JO. Nitric oxide signaling and regulation in the cardiovascular system: recent advances. *Pharmacol Rev*. 2024;76(6):1038–1062. doi:10.1124/pharmrev.124.001060
150. Wang XL, Zhang L, Youker K, et al. Free fatty acids inhibit insulin signaling-stimulated endothelial nitric oxide synthase activation through upregulating PTEN or inhibiting Akt kinase. *Diabetes*. 2006;55(8):2301–2310. doi:10.2337/db05-1574
151. Libby P, Buring JE, Badimon L, et al. Atherosclerosis. *Nat Rev Dis Primers*. 2019;5(1):56. doi:10.1038/s41572-019-0106-z
152. Liu Q, Cheng Z, Huang B, et al. Palmitic acid promotes endothelial-to-mesenchymal transition via activation of the cytosolic DNA-sensing cGAS-STING pathway. *Arch Biochem Biophys*. 2022;727:109321. doi:10.1016/j.abb.2022.109321
153. Seeger FH, Haendeler J, Walter DH, et al. p38 mitogen-activated protein kinase downregulates endothelial progenitor cells. *Circulation*. 2005;111(9):1184–1191. doi:10.1161/01.Cir.0000157156.85397.A1
154. Jiang H, Liang C, Liu X, et al. Palmitic acid promotes endothelial progenitor cells apoptosis via p38 and JNK mitogen-activated protein kinase pathways. *Atherosclerosis*. 2010;210(1):71–77. doi:10.1016/j.atherosclerosis.2009.10.032
155. Murphy JE, Tedbury PR, Homer-Vanniasinkam S, et al. Biochemistry and cell biology of mammalian scavenger receptors. *Atherosclerosis*. 2005;182(1):1–15. doi:10.1016/j.atherosclerosis.2005.03.036
156. Ishiyama J, Taguchi R, Yamamoto A, et al. Palmitic acid enhances lectin-like oxidized LDL receptor (LOX-1) expression and promotes uptake of oxidized LDL in macrophage cells. *Atherosclerosis*. 2010;209(1):118–124. doi:10.1016/j.atherosclerosis.2009.09.004
157. Murphy DL, Lesch KP. Targeting the murine serotonin transporter: insights into human neurobiology. *Nat Rev Neurosci*. 2008;9(2):85–96. doi:10.1038/nrn2284
158. Caruso G, Fresta CG, Grasso M, et al. Inflammation as the common biological link between depression and cardiovascular diseases: can carnosine exert a protective role? *Curr Med Chem*. 2020;27(11):1782–1800. doi:10.2174/0929867326666190712091515
159. Ma Y, Liang X, Li C, et al. 5-HT(2A) receptor and 5-HT degradation play a crucial role in atherosclerosis by modulating macrophage foam cell formation, vascular endothelial cell inflammation, and hepatic steatosis. *J Atheroscler Thromb*. 2022;29(3):322–336. doi:10.5551/jat.58305
160. Luo Y, Duan H, Qian Y, et al. Macrophagic CD146 promotes foam cell formation and retention during atherosclerosis. *Cell Research*. 2017;27(3):352–372. doi:10.1038/cr.2017.8
161. Duan H, Jing L, Xiang J, et al. CD146 associates with Gp130 to control a macrophage pro-inflammatory program that regulates the metabolic response to obesity. *Adv Sci*. 2022;9(13):2103719. doi:10.1002/advs.202103719
162. Cheng G, Zheng L. Regulation of the apolipoprotein M signaling pathway: a review. *J Recept Signal Transduct Res*. 2022;42(3):285–292. doi:10.1080/10799893.2021.1924203
163. Zhang XY, Dong X, Zheng L, et al. Specific tissue expression and cellular localization of human apolipoprotein M as determined by in situ hybridization. *Acta Histochem*. 2003;105(1):67–72. doi:10.1078/0065-1281-00687
164. Luo G, Zhang X, Mu Q, et al. Expression and localization of apolipoprotein M in human colorectal tissues. *Lipids Health Dis*. 2010;9:102. doi:10.1186/1476-511x-9-102
165. Christoffersen C, Obinata H, Kumaraswamy SB, et al. Endothelium-protective sphingosine-1-phosphate provided by HDL-associated apolipoprotein M. *Proc Natl Acad Sci U S A*. 2011;108(23):9613–9618. doi:10.1073/pnas.1103187108
166. Mousa H, Elrayess MA, Diboun I, et al. Metabolomics profiling of vitamin D status in relation to dyslipidemia. *Metabolites*. 2022;12(8). doi:10.3390/metabo12080771
167. Elsøe S, Ahnström J, Christoffersen C, et al. Apolipoprotein M binds oxidized phospholipids and increases the antioxidant effect of HDL. *Atherosclerosis*. 2012;221(1):91–97. doi:10.1016/j.atherosclerosis.2011.11.031
168. Wolfrum C, Poy MN, Stoffel M. Apolipoprotein M is required for prebeta-HDL formation and cholesterol efflux to HDL and protects against atherosclerosis. *Nat Med*. 2005;11(4):418–422. doi:10.1038/nm1211
169. Ali FY, Armstrong PC, Dhanji AR, et al. Antiplatelet actions of statins and fibrates are mediated by PPARs. *Arterioscler Thromb Vasc Biol*. 2009;29(5):706–711. doi:10.1161/atvbaha.108.183160
170. Yeung J, Adili R, Yamaguchi A, et al. Omega-6 DPA and its 12-lipoxygenase-oxidized lipids regulate platelet reactivity in a nongenomic PPARα-dependent manner. *Blood Adv*. 2020;4(18):4522–4537. doi:10.1182/bloodadvances.2020002493
171. Yang ZH, Emma-Okon B, Remaley AT. Dietary marine-derived long-chain monounsaturated fatty acids and cardiovascular disease risk: a mini review. *Lipids Health Dis*. 2016;15(1):201. doi:10.1186/s12944-016-0366-5
172. Shramko VS, Striukova EV, Polonskaya YV, et al. Associations of antioxidant enzymes with the concentration of fatty acids in the blood of men with coronary artery atherosclerosis. *J Pers Med*. 2021;11(12). doi:10.3390/jpm11121281
173. Ebbesson SO, Tejero ME, López-Alvarenga JC, et al. Individual saturated fatty acids are associated with different components of insulin resistance and glucose metabolism: the GOCADAN study. *Int J Circumpolar Health*. 2010;69(4):344–351. doi:10.3402/ijch.v69i4.17669
174. Li Y, Hruby A, Bernstein AM, et al. Saturated fats compared with unsaturated fats and sources of carbohydrates in relation to risk of coronary heart disease: a prospective cohort study. *J Am Coll Cardiol*. 2015;66(14):1538–1548. doi:10.1016/j.jacc.2015.07.055
175. S AIS, B CA, S AJ. Changes in plasma free fatty acids associated with type-2 diabetes. *Nutrients*. 2019;11(9). doi:10.3390/nu11092022

176. Alsharari ZD, Risérus U, Leander K, et al. Serum fatty acids, desaturase activities and abdominal obesity - a population-based study of 60-year old men and women. *PLoS One*. 2017;12(1):e0170684. doi:10.1371/journal.pone.0170684
177. Bucalossi A, Mori S. Fatty acid composition of adipose tissue in ischemic heart disease and stroke. *Gerontol Clin*. 1972;14(6):339–345. doi:10.1159/000245419
178. Insull W, Lang P, Hsi B. Adipose tissue fatty acids and extent of coronary atherosclerosis. In: Proceedings of the Circulation; Philadelphia, PA: Lippincott Williams & Wilkins 1968:19106.
179. Lee K, Shaper A, Scott R, et al. Geographic studies pertaining to arteriosclerosis: comparison of fatty acid patterns of adipose tissue and plasma lipids in East Africans with those of North American white and Negro groups. *Arch Pathol*. 1962;74:481–488.
180. Lopaschuk GD, Ussher JR, Folmes CD, et al. Myocardial fatty acid metabolism in health and disease. *Physiol Rev*. 2010;90(1):207–258. doi:10.1152/physrev.00015.2009
181. Tomata Y, Wang Y, Hägg S, et al. Fatty acids and frailty: a mendelian randomization study. *Nutrients*. 2021;13(10). doi:10.3390/nu13103539
182. Cetrullo S, Tantini B, Flamigni F, et al. Antiapoptotic and antiautophagic effects of eicosapentaenoic acid in cardiac myoblasts exposed to palmitic acid. *Nutrients*. 2012;4(2):78–90. doi:10.3390/nu4020078
183. Dyntar D, Eppenberger-Eberhardt M, Maedler K, et al. Glucose and palmitic acid induce degeneration of myofibrils and modulate apoptosis in rat adult cardiomyocytes. *Diabetes*. 2001;50(9):2105–2113. doi:10.2337/diabetes.50.9.2105
184. Lemaitre RN, Jensen PN, Hoofnagle A, et al. Plasma ceramides and sphingomyelins in relation to heart failure risk. *Circ Heart Fail*. 2019;12 (7):e005708. doi:10.1161/circheartfailure.118.005708
185. Hooper L, Martin N, Jimoh OF, et al. Reduction in saturated fat intake for cardiovascular disease. *Cochrane Database Syst Rev*. 2020;5(5): Cd011737. doi:10.1002/14651858.CD011737.pub2
186. Wang DD, Li Y, Chiuve SE, et al. Association of specific dietary fats with total and cause-specific mortality. *JAMA Intern Med*. 2016;176 (8):1134–1145. doi:10.1001/jamainternmed.2016.2417
187. Duda MK, O'shea KM, Stanley WC. omega-3 polyunsaturated fatty acid supplementation for the treatment of heart failure: mechanisms and clinical potential. *Cardiovasc Res*. 2009;84(1):33–41. doi:10.1093/cvr/cvp169
188. Cerf ME, Louw J. Islet cell response to high fat programming in neonate, weanling and adolescent Wistar rats. *JOP*. 2014;15(3):228–236. doi:10.6092/1590-8577/1534
189. Taegtmeyer H, Stanley WC. Too much or not enough of a good thing? Cardiac glucolipotoxicity versus lipoprotection. *J Mol Cell Cardiol*. 2011;50(1):2–5. doi:10.1016/j.yjmcc.2010.09.014
190. Dixon SJ, Lemberg KM, Lamprecht MR, et al. Ferroptosis: an iron-dependent form of nonapoptotic cell death. *Cell*. 2012;149(5):1060–1072. doi:10.1016/j.cell.2012.03.042
191. Stockwell BR, Friedmann Angeli JP, Bayir H, et al. Ferroptosis: a regulated cell death nexus linking metabolism, redox biology, and disease. *Cell*. 2017;171(2):273–285. doi:10.1016/j.cell.2017.09.021
192. Jiang X, Stockwell BR, Conrad M. Ferroptosis: mechanisms, biology and role in disease. *Nat Rev Mol Cell Biol*. 2021;22(4):266–282. doi:10.1038/s41580-020-00324-8
193. Ke C, Pan CW, Zhang Y, et al. Metabolomics facilitates the discovery of metabolic biomarkers and pathways for ischemic stroke: a systematic review. *Metabolomics*. 2019;15(12):152. doi:10.1007/s11306-019-1615-1
194. Fielding CJ, Fielding PE. Cholesterol transport between cells and body fluids. Role of plasma lipoproteins and the plasma cholesterol esterification system. *Med Clin North Am*. 1982;66(2):363–373. doi:10.1016/s0025-7125(16)31425-0
195. Satizabal CL, Samieri C, Davis-Plourde KL, et al. APOE and the association of fatty acids with the risk of stroke, coronary heart disease, and mortality. *Stroke*. 2018;49(12):2822–2829. doi:10.1161/strokeaha.118.022132
196. Yamagishi K, Folsom AR, Steffen LM, et al. Plasma fatty acid composition and incident ischemic stroke in middle-aged adults: the Atherosclerosis Risk in Communities (ARIC) Study. *Cerebrovasc Dis*. 2013;36(1):38–46. doi:10.1159/000351205
197. Thaler JP, Yi CX, Schur EA, et al. Obesity is associated with hypothalamic injury in rodents and humans. *J Clin Invest*. 2012;122(1):153–162. doi:10.1172/jci59660
198. Moraes JC, Coope A, Morari J, et al. High-fat diet induces apoptosis of hypothalamic neurons. *PLoS One*. 2009;4(4):e5045. doi:10.1371/journal.pone.0005045
199. Ricchi M, Odoardi MR, Carulli L, et al. Differential effect of oleic and palmitic acid on lipid accumulation and apoptosis in cultured hepatocytes. *J Gastroenterol Hepatol*. 2009;24(5):830–840. doi:10.1111/j.1440-1746.2008.05733.x
200. Mayer CM, Belsham DD. Palmitate attenuates insulin signaling and induces endoplasmic reticulum stress and apoptosis in hypothalamic neurons: rescue of resistance and apoptosis through adenosine 5' monophosphate-activated protein kinase activation. *Endocrinology*. 2010;151 (2):576–585. doi:10.1210/en.2009-1122
201. Truran S, Karamanova N, Serrano G, et al. Palmitic acid-induced endothelial dysfunction in human leptomeningeal and adipose arterioles. *Circulation*. 2015;132(suppl_3):A18245–A18245.
202. Karamanova N, Truran S, Madine J, et al. Medin amyloid, but not β-amyloid, induces pro-inflammatory signaling in endothelial cells that is synergistic with palmitic acid. *Circulation*. 2017;136(suppl_1):A14270–A14270.
203. Posey KA, Clegg DJ, Printz RL, et al. Hypothalamic proinflammatory lipid accumulation, inflammation, and insulin resistance in rats fed a high-fat diet. *Am J Physiol Endocrinol Metab*. 2009;296(5):E1003–1012. doi:10.1152/ajpendo.90377.2008
204. Milanski M, Degasperi G, Coope A, et al. Saturated fatty acids produce an inflammatory response predominantly through the activation of TLR4 signaling in hypothalamus: implications for the pathogenesis of obesity. *J Neurosci*. 2009;29(2):359–370. doi:10.1523/jneurosci.2760-08.2009
205. Lu Z, Liu S, Lopes-Virella MF, et al. LPS and palmitic acid Co-upregulate microglia activation and neuroinflammatory response. *Compr Psychoneuroendocrinol*. 2021;6:100048. doi:10.1016/j.cpnec.2021.100048
206. Zhang Y, Dong L, Yang X, et al. α-Linolenic acid prevents endoplasmic reticulum stress-mediated apoptosis of stearic acid lipotoxicity on primary rat hepatocytes. *Lipids Health Dis*. 2011;10:81. doi:10.1186/1476-511x-10-81
207. Ng YW, Say YH. Palmitic acid induces neurotoxicity and gliatoxicity in SH-SY5Y human neuroblastoma and T98G human glioblastoma cells. *PeerJ*. 2018;6:e4696. doi:10.7717/peerj.4696

208. Xue X, Li F, Cai M, et al. Interactions between endoplasmic reticulum stress and autophagy: implications for apoptosis and neuroplasticity-related proteins in palmitic acid-treated prefrontal cells. *Neural Plast*. 2021;2021:8851327. doi:10.1155/2021/8851327
209. Khan M, Rutten BPF, Kim MO. MST1 regulates neuronal cell death via JNK/Casp3 signaling pathway in HFD mouse brain and HT22 cells. *Int J Mol Sci*. 2019;20(10). doi:10.3390/ijms20102504
210. Hernández-Cáceres MP, Cereceda K, Hernández S, et al. Palmitic acid reduces the autophagic flux in hypothalamic neurons by impairing autophagosome-lysosome fusion and endolysosomal dynamics. *Mol Cell Oncol*. 2020;7(5):1789418. doi:10.1080/23723556.2020.1789418
211. Fu CN, Wei H, Gao WS, et al. Obesity increases neuropathic pain via the AMPK-ERK-NOX4 pathway in rats. *Aging*. 2021;13(14):18606–18619. doi:10.18632/aging.203305
212. Deng W, Mandeville E, Terasaki Y, et al. Transcriptomic characterization of microglia activation in a rat model of ischemic stroke. *J Cereb Blood Flow Metab*. 2020;40(1_suppl):S34–s48. doi:10.1177/0271678x20932870
213. Zhou YD. Glial regulation of energy metabolism. *Adv Exp Med Biol*. 2018;1090:105–121. doi:10.1007/978-981-13-1286-1_6
214. Yang C, Sui G, Wang L, et al. MiR-124 prevents the microglial proinflammatory response by inhibiting the activities of TLR4 and downstream NLRP3 in palmitic acid-treated BV2 cells. *J Mol Neurosci*. 2022;72(3):496–506. doi:10.1007/s12031-021-01921-8
215. Chowen JA, Frago LM, Fernández-Alfonso MS. Physiological and pathophysiological roles of hypothalamic astrocytes in metabolism. *J Neuroendocrinol*. 2019;31(5):e12671. doi:10.1111/jne.12671
216. Joyal JS, Sun Y, Gantner ML, et al. Retinal lipid and glucose metabolism dictates angiogenesis through the lipid sensor Ffar1. *Nat Med*. 2016;22(4):439–445. doi:10.1038/nm.4059