Lipids in Health and Disease

REVIEW

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Lipids dysregulation in diseases: core concepts, targets and treatment strategies

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Abstract

Lipid metabolism is a well-regulated process essential for maintaining cellular functions and energy homeostasis. Dysregulation of lipid metabolism is associated with various conditions, including cardiovascular diseases, neurodegenerative disorders, and metabolic syndromes. This review explores the mechanisms underlying lipid metabolism, emphasizing the roles of key lipid species such as triglycerides, phospholipids, sphingolipids, and sterols in cellular physiology and pathophysiology. It also examines the genetic and environmental factors contributing to lipid dysregulation and the challenges of diagnosing and managing lipid-related disorders. Recent advancements in lipid-lowering therapies, including PCSK9 inhibitors, ezetimibe, bempedoic acid, and olpasiran, provide promising treatment options. However, these advancements are accompanied by challenges related to cost, accessibility, and patient adherence. The review highlights the need for personalized medicine approaches to address the interplay between genetics and environmental factors in lipid metabolism. As lipidomics and advanced diagnostic tools continue to progress, a deeper understanding of lipid-related disorders could pave the way for more effective therapeutic strategies.

Keywords Lipid metabolism, Dyslipidemia, Cardiovascular disease (CVD), Lipidomics, Triglycerides, Phospholipids, Cholesterol

Introduction

Lipids are organic molecules characterized by their hydrophobic nature, exhibiting poor solubility in water but excellent solubility in organic solvents. In the animal kingdom, lipids play critical roles in energy storage, thermal insulation, cellular membrane formation, and acting as chemical messengers. However, elevated lipid levels in the blood can lead to fat deposition in arterial walls, a condition associated with vascular complications such as atherosclerosis, stroke, and heart disease [1–3].

Disruptions in lipid metabolism, often stemming from enzymatic dysfunction or insufficient enzyme production, can result in excessive lipid accumulation. This retention leads to persistent cellular and tissue damage, particularly affecting the central and peripheral nervous systems. Such damage is implicated in metabolic disorders, including Gaucher's disease, Tay-Sachs disease, and

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Niemann-Pick disease (NPD) [4]. Obesity, characterized by abnormal fat accumulation, significantly increases the risk of heart disease, diabetes, and hypertension [5]. Additionally, alterations in the composition of the intestinal microbiome have been linked to accelerated liver fat buildup, contributing to obesity and metabolic diseases [6]. Notably, approximately 50% of deaths related to cardiovascular diseases can be attributed to metabolic imbalances, with obesity, hyperglycemia, atherogenic dyslipidemia, and hypertension being key risk factors [7].

Metabolic dysfunction often arises from pathophysiological interactions that lead to abnormal and detrimental metabolic activity. Obesity-related metabolic disorders, identifiable in early childhood, manifest through various conditions, including infertility, hypothyroidism, nonalcoholic steatohepatitis, hormone imbalances, and diabetes [8, 9]. Insulin resistance, a growing concern associated with lipid metabolism dysfunction, necessitates advancements in pharmaceutical research and diagnostic tools [10]. Excessive consumption of saturated fats and deficiencies in essential lipids, such as polyunsaturated fats and phospholipids, contribute to inflammation and glucose-insulin imbalance. Furthermore, specific lipid mediators, such as lipoxin A4, have been identified in chronic diseases, including periodontal conditions [11]. The National Institute of Neurological Disorders and Stroke highlights that the excessive accumulation of fat significantly contributes to health complications, including tissue damage and diseases affecting the liver, brain, bone marrow, peripheral nervous system, and spleen.

Lipid dysregulation refers to disturbances in lipid metabolism caused by genetic factors, dietary habits, lifestyle, and underlying diseases. Conditions such as dyslipidemia, characterized by elevated cholesterol levels, significantly increase the risk of cardiovascular disease [12, 13]. This review highlights the need for a multifaceted approach to treatment, combining pharmacological interventions, lifestyle modifications, and personalized medicine. Such a holistic perspective aims to improve patient outcomes and advance the field of lipid metabolism and its associated health conditions.

This review aims to provide a comprehensive overview of lipid dysregulation, its role in various diseases, and the potential for targeted therapeutic strategies. It explores core concepts and clinical relevance, emphasizing the mechanisms underlying lipid-related disorders. Understanding the molecular and physiological basis of lipid dysregulation could pave the way for innovative pharmacological interventions and lifestyle modifications to effectively address these disorders. Furthermore, this review highlights the need for a multifaceted approach to treatment, combining pharmacological interventions, lifestyle modifications, and personalized medicine. Such a holistic perspective aims to improve patient outcomes and advance the field of lipid metabolism and its associated health conditions.

Causes and consequences of lipid dysregulation

The reduction in elevated LDL cholesterol levels rarely exceeds 10%, regardless of the treatment methods employed. The most significant improvement is achieved by reducing the intake of saturated fatty acids, particularly those derived from animal fats [14]. Due to the minimal effect of dietary cholesterol, current U.S. guidelines do not recommend restricting cholesterol intake [15]. Lifestyle modifications, either alone or in combination with lipid-lowering strategies, have a greater impact on elevated triglyceride levels. For instance, limiting alcohol consumption and reducing the intake of fast-absorbing carbohydrates can lead to a reduction in triglyceride levels by over 50%. Regular physical activity further enhances lipid profiles. While the direct impact on fat proportions may be moderate in some cases, these adjustments positively influence the overall risk profile [16].

For individuals at high cardiovascular risk, adherence to a Mediterranean diet rich in olive oil and almonds has been shown to lower the relative risk by 30%. Additionally, nut consumption has demonstrated LDL cholesterol reduction and an overall improvement in lipid profiles, contributing to decreased cardiovascular risk [17].

Imbalances in the secondary metabolism of lipids are associated with several diseases. The most common clinical conditions include diabetes mellitus, hypothyroidism (characterized by elevated LDL cholesterol), renal diseases (manifesting as hypertriglyceridemia or mixed hyperlipoproteinemia; see Table 1), and cholestatic liver disorders [18, 19]. Furthermore, lipid metabolism abnormalities have been linked to other medical conditions such as lymphoma, Cushing syndrome, and porphyria [20].

When lipid metabolism dysfunction results from an underlying condition, the primary treatment approach should focus on managing the root cause. However, individuals with chronic diseases like diabetes or renal dysfunction often face challenges in addressing the underlying condition effectively. As a result, they frequently experience symptoms stemming from both primary and secondary lipid metabolism abnormalities [25].

Hypertriglyceridemia

Triglyceride levels are often significantly elevated in isolated hypertriglyceridemia, while LDL cholesterol levels show only moderate increases. Total cholesterol levels may also be elevated in some cases. Isolated hypertriglyceridemia generally responds well to lifestyle

Table 1 Lipoproteinemia types and management

Type	Description	Lipid Profile	Associated CVD Risks	Genetic Basis	Prevalence	Diagnostic Criteria	Management Strategies
Type I Hyperlipoproteinemia [21]	Rare genetic disorder characterized by elevated chylomicrons due to lipoprotein lipase (LPL) deficiency.	Elevated chylomicrons, normal LDL, VLDL levels	Risk of pancreatitis, minimal direct CVD risk	LPL gene mutation	~1 in 1,000,000	Elevated chylomicrons on fasting lipid profile; LPL activity assay	Low-fat diet, enzyme replacement therapy, and omega-3 fatty acids
Type IIa Hyperlipoproteinemia [22]	Elevated LDL cholesterol due to impaired LDL receptor function.	Elevated LDL, normal VLDL, chylomicrons	High risk of atherosclerosis, CAD	LDLR gene mutation	1 in 500 in the general population	Elevated LDL cholesterol; Genetic testing for LDLR mutations	Statins, lifestyle modification, PCSK9 inhibitors
Type IIb Hyperlipoproteinemia [22]	Combined hyperlipidemia with elevated LDL and VLDL levels.	Elevated LDL and VLDL, normal chylomicrons	High risk of atherosclerosis, CAD, and stroke	Variants in APOB, LDLR genes	1 in 1,000 in the general population	Elevated LDL and VLDL levels; APOB, LDLR gene analysis	Statins, fibrates, niacin, lifestyle changes
Type III Hyperlipoproteinemia [23]	Dysbetalipoproteinemia with elevated IDL due to defective APOE.	Elevated IDL, elevated cholesterol and triglycerides	Increased risk of atherosclerosis, CAD, stroke	APOE gene mutation	1 in 10,000 in the general population	Elevated IDL on lipid profile; APOE gene analysis	Statins, lifestyle changes, fibrates, and niacin
Type IV Hyperlipoproteinemia [23]	Elevated VLDL levels due to overproduction of VLDL or impaired clearance.	Elevated VLDL, normal LDL, elevated triglycerides	Risk of pancreatitis, variable CVD risk	Genetic factors, sometimes secondary	Common in the general population	Elevated VLDL and triglycerides; Lipoprotein electrophoresis	Fibrates, lifestyle modification, niacin, statins if needed
Type V Hyperlipoproteinemia [24]	Elevated chylomicrons and VLDL due to combined LPL deficiency and overproduction of VLDL.	Elevated chylomicrons and VLDL, normal LDL	High risk of pancreatitis and CVD	LPL gene mutation, secondary causes	Rare	Elevated chylomicrons and VLDL; LPL activity assay	Low-fat diet, fibrates, addressing secondary causes, omega-3 fatty acids

modifications, similar to mixed hyperlipoproteinemia [26]. However, predicting whether a patient will respond positively or negatively remains challenging due to insufficient conclusive studies. The detection threshold for hypertriglyceridemia is lower in individuals at higher risk for atherosclerosis compared to generally healthy individuals [27]. When triglyceride concentrations persist above 400 mg/dL despite lifestyle interventions, fibrates may be prescribed [28]. Fenofibrate and gemfibrozil are often recommended as first-line therapies [29]. Omega-3 fatty acids can also be administered separately or in combination with other treatments as needed [30]. Statins are typically less effective for treating hypertriglyceridemia alone, especially when LDL cholesterol levels are already low [31]. However, patients diagnosed with atherosclerosis should receive statins regardless of their LDL levels [32].

LDL hypercholesterolemia

According to European guidelines, LDL cholesterol targets should be tailored to an individual's overall risk profile. If lifestyle modifications fail to achieve target levels, the initial step in medical intervention involves statin therapy [33]. When treatment goals are not reached within 4 to 6 weeks, dosage adjustments or additional interventions may be necessary. For high-risk individuals, lifestyle modifications and statin therapy should be initiated simultaneously. If statins alone are insufficient to achieve desired LDL levels, ezetimibe is recommended as an add-on therapy [34]. In cases where the combination of statins and ezetimibe fails, PCSK9 inhibitors may be considered as an alternative treatment option [35]. For patients with atherosclerosis and resistant LDL hypercholesterolemia, repeated lipid apheresis may serve as a final option [36]. Other statins such as lovastatin, fluvastatin, pravastatin, rosuvastatin, and pitavastatin are used less frequently. Fluvastatin and pravastatin are associated with fewer side effects compared to atorvastatin and simvastatin [37]. Rosuvastatin, known for its potency in reducing LDL cholesterol levels, has shown promising results in preclinical studies, with ongoing clinical trials providing further insights [37]. Acute coronary syndrome (ACS) is a distinct medical condition. Preliminary research suggests that early administration of high-dose statins may improve outcomes in ACS patients, potentially by mechanisms independent of LDL cholesterol's impact on endothelial function [35]. However, these findings should be interpreted cautiously, as most guidelines recommend high-dose statins for ACS management.

Mixed hyperlipoproteinemia

Mixed hyperlipoproteinemia, characterized by elevated levels of both LDL cholesterol and triglycerides, is the most common lipid metabolism disorder among individuals with diabetes, primarily due to its association with metabolic syndrome [38]. Lifestyle modification remains the cornerstone of management [39]. If lifestyle changes and statin therapy fail to normalize lipid levels or triglyceride concentrations, a combination treatment approach may be necessary. Although statins can be combined with omega-3 fatty acids or fibrates, the effectiveness of these combinations has been inconsistent in endpoint trials [40]. Inadequate trial design limits definitive conclusions, despite both classes of medications demonstrating cardiovascular risk reduction in individual therapy studies. At our facility, we employ a combination of statins with fibrates or omega-3 fatty acids for patients at extremely high cardiovascular risk and with concurrent lipid metabolism disorders, only after all other methods for reducing LDL cholesterol have been exhausted [41, 42].

Lipid dysregulation plays a crucial role in various diseases

Fluctuations in lipid levels significantly impact health, underscoring their critical role in disease development. High-density lipoprotein (HDL), often termed "good cholesterol," facilitates the removal of harmful lipids. In contrast, the accumulation of low-density lipoprotein (LDL) and triglycerides, categorized as "bad lipids," damages arterial walls and contributes to cardiovascular diseases [43]. Recent studies have linked lipid metabolism abnormalities to over 80 diseases, highlighting their complex biological implications. These investigations explore metabolic pathways, including nonlysosomal sphingolipids and acylceramides, to better understand lipid biology [44, 45]. Fredrickson's classification system categorizes lipid metabolism disorders into five types based on their underlying pathways and associated health conditions [46]. Hyperlipidemia, as described by Natesan and Kim (2021), refers to the pathological elevation of lipids in the bloodstream, which increases the risk of severe health conditions [47]. This group of disorders is characterized by elevated levels of undesirable lipids, with the classification of specific metabolic diseases dependent on abnormalities in different lipoprotein classes (Fig. 1). Structural defects in lipoproteins, apolipoproteins, or lipid transfer proteins are often implicated in these disorders. A key regulatory role in lipid metabolism is played by peroxisome proliferator-activated receptors (PPARs), also known as nuclear fatty acid receptors. These receptors influence pathways associated with obesity-related metabolic disorders such as coronary artery disease, hyperlipidemia, and insulin resistance. PPARs have also been explored as therapeutic targets for managing these diseases [48, 49]. Postmenopausal women are particularly susceptible to

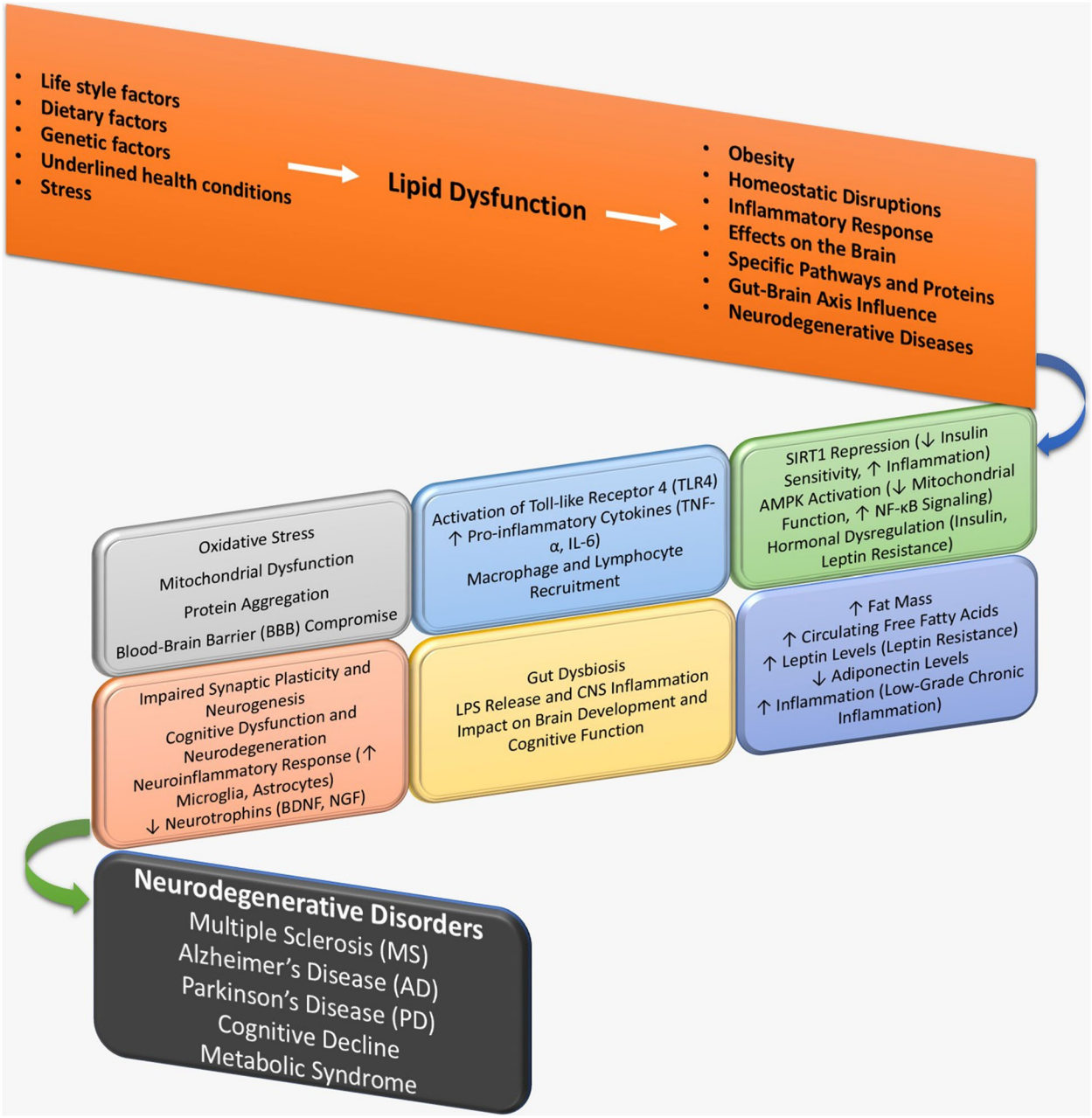

Fig. 1 Lipid metabolism disorder

lipid metabolism disorders, including osteoporosis and atherosclerosis, which are pressing global health concerns [50]. Excessive lipid accumulation in muscle fibers is linked to the development of myopathy and carnitine deficiency, further emphasizing the broad implications of lipid dysregulation [51]. Dysregulation in lipid metabolic pathways is associated with numerous diseases, including conditions resulting from excessive lipid accumulation such as xanthomas, Bassen-Kornzweig syndrome, chylomicronemia syndrome, familial lipoprotein lipase deficiency, Niemann-Pick disease (types A and B), GM1 and GM2 gangliosidoses, methylmalonic acidemia, and Gaucher disease [52]. Acquired hyperlipidemia, a significant contributor to lipid dysregulation, is often triggered by secondary factors such as diabetes, excessive alcohol consumption, hypothyroidism, renal diseases, nephrotic

syndrome, or long-term use of medications like diuretics, estrogens, and β-blockers [47].

Obesity-related diseases and neurodegenerative disorders

Obesity exerts a multifaceted impact on physiological functions across various organs, culminating in a general decline in health. In the brain, obesity precipitates a spectrum of homeostatic imbalances, including heightened cellular oxidative burden, swelling, protein accumulation, disrupted mitochondrial function, hormonal dysregulation, insulin resistance, and impaired blood-brain barrier (BBB) integrity [53]. These disruptions diversely affect synaptic plasticity, neurogenesis, and neuronal survival, resulting in cognitive impairments [54]. Early-life obesity induced by diet has enduring effects due to changes in the innate defense system, extending beyond addressing metabolic issues. Stearic acid, via Toll-like receptor 4 (TLR4), alters chromatin structure, enhancing binding site availability for activator protein-1, which signals myeloid cells to shift from oxidative phosphorylation to glycolysis, thereby initiating pro-inflammatory cytokine production [55].

Chronic inflammation in obesity, driven by hypertrophic adipocytes, triggers endoplasmic reticulum stress, activation of inflammatory pathways, and insulin resistance [56]. This persistent inflammation is marked by altered cytokine and adipokine profiles from dysfunctional adipose tissue, recruitment of macrophages and lymphocytes, which exacerbates insulin resistance and inflammation [57]. Insulin-resistant adipocytes elevate circulating free fatty acids, activating TLR4 in B cells and leading to the production of pro-inflammatory cytokines such as TNF-α and IL-6 [58]. Leptin and adiponectin, primarily produced by adipocytes, modulate inflammation and play pivotal roles in glucose and lipid metabolism as well as energy homeostasis [59]. With increased fat mass, leptin levels rise while adiponectin decreases, leading to leptin resistance, lipid accumulation, lipotoxicity, and insulin resistance [60]. Furthermore, diminished activation of AMP-activated protein kinase (AMPK), a crucial regulator of cellular metabolism and energy homeostasis, is seen, impacting glucose and free fatty acid uptake, cell cycle progression, mRNA stability, and apoptosis [61]. In obesity, high-fat diet studies show decreased AMPK activation in white adipose tissue (WAT), heart, and liver, associated with mitochondrial dysfunction, reduced fatty acid oxidation, and activation of NF-κB signaling, contributing to metabolic inflammation and oxidative stress [62]. Furthermore, hyperleptinemia and decreased cerebrospinal fluid leptin levels suggest impaired leptin transport across the BBB, contributing to leptin resistance [63].

Leptin is crucial for immune system performance, influencing immune cells such as $CD4^+$, $CD8^+$ T cells, regulatory T cells (Treg), natural killer cells (NK), and monocytes or macrophages [64]. Adiponectin, inversely related to adiposity, exhibits a plethora of beneficial properties including insulin-sensitizing, anti-inflammatory, anti-apoptotic, anti-atherosclerotic, and neuroprotective properties [65]. In the context of obesity, adiponectin reduction is influenced by mechanisms such as DNA methylation, where DNA hypermethylation in adipocytes leads to the downregulated adiponectin gene expression [66]. Sirtuin 1 (SIRT1), a NAD+-dependent deacetylase, is crucial for regulating metabolic responses to nutrient availability. It supports fatty acid β-oxidation, maintains cholesterol and bile acid levels, and aids in neuronal survival and differentiation [67]. However, SIRT1 is repressed in obesity, which contributes to insulin resistance, non-alcoholic fatty liver disease, and imbalance in energy balance [68].

Neurotrophins like nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) are important for nerve growth and survival and also influence glucose, lipid, and energy homeostasis. Lower concentrations of NGF and BDNF in metabolic syndrome conditions suggest their participation in atherosclerosis and metabolic dysfunction [69]. Gene mutations affecting BDNF or its receptor Trkβ can lead to excessive eating and obesity. BDNF gene expression is influenced by nutritional, glucose levels, and anorexigenic hormones, thereby affecting satiety regulation [70]. Obesity induces chronic low-grade inflammation, affecting brain metabolism, BBB integrity, and cognitive functions. Overconsumption of high-carbohydrate and high-fat foods in obesity impairs cerebral glucose metabolism, contributing to neurodegenerative diseases [71]. Obesity-related inflammation and insulin resistance disrupt insulin transporters at the BBB, facilitating leukocyte infiltration into the central nervous system (CNS), and promoting neurodegenerative diseases [72]. Increased expression of microglia and astrocytic markers, along with elevated cytokine levels in high-fat diet (HFD) mice, highlights the inflammatory response in the CNS [73]. Mitochondrial dysfunction in obesity affects brain energy demand, contributing to cognitive decline and neurodegeneration [74]. HFD-induced mitochondrial disturbances reduce oxidative capacity in the brain cortex, affecting synaptic plasticity and energy metabolism, leading to cognitive impairment [75]. Increased lipid peroxidation, ROS production, and decreased ATP production further exacerbate cognitive decline [76]. The gut-brain axis is crucial in obesity-related CNS complications. Gut microbiota diversity significantly impacts brain development and cognitive function. HFD-induced changes in gut microbiota are

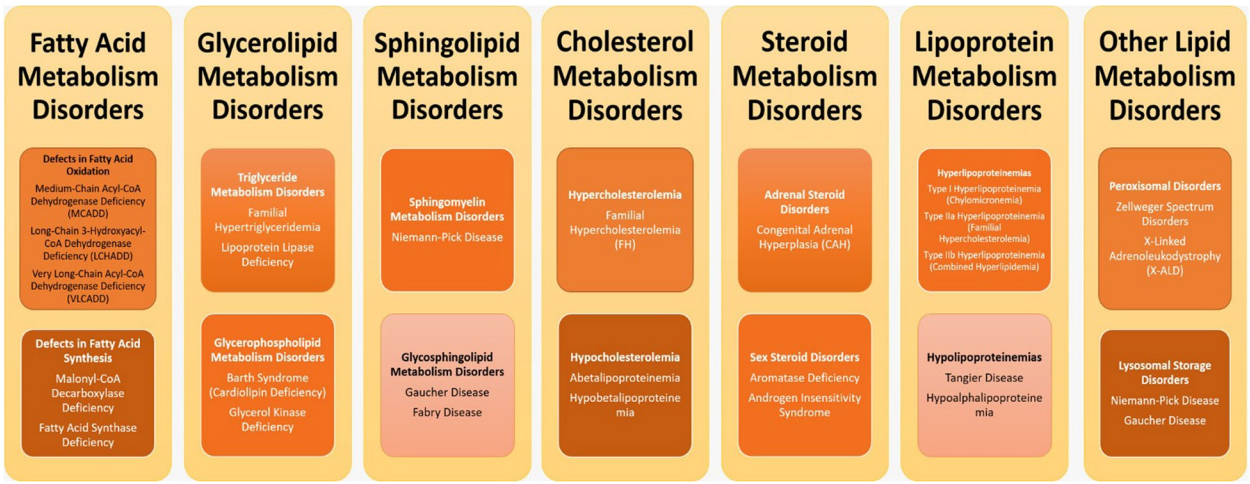

Fig. 2 Pathophysiological pathway from obesity to neurodegenerative diseases

linked to reduced synaptic plasticity and cognitive functions [77]. Obesity-associated gut dysbiosis releases bacterial toxins like lipopolysaccharide (LPS), affecting CNS inflammation and cognitive functions (Fig. 2) [78].

Dyslipidemia and Cardiovascular Disease (CVD)

Cardiovascular diseases (CVD) remain the top cause of morbidity and mortality globally, with dyslipidemia being a critical risk factor [79]. Dyslipidemia, characterized by aberrant lipid levels in the bloodstream, is primarily identified by elevated cholesterol levels, known as hypercholesterolemia [79]. Among the various lipoproteins, low-density lipoprotein (LDL), which contains apolipoprotein B (ApoB), predominates in plasma and is crucial for cholesterol transport to blood vessel walls [80]. Elevated LDL cholesterol is a significant hallmark of dyslipidemia and closely linked to an increased risk of atherosclerotic cardiovascular disease (ASCVD). Extensive epidemiological, clinical, and experimental research underscores the significance of LDL cholesterol, along with its oxidized forms, as principal drivers of atherosclerosis and its progression. Consequently, reducing LDL cholesterol levels has become a cornerstone of both the treatment and prevention strategies for ASCVD [81, 82].

The effectiveness of lipid-lowering therapies in managing LDL cholesterol levels is well-documented. Statins, which inhibit hepatic cholesterol synthesis, are the most frequently prescribed agents and are considered the cornerstone of LDL cholesterol reduction [83]. These medications have demonstrated substantial benefits in reducing cardiovascular disease incidence. When statins alone do not achieve optimal LDL cholesterol levels, additional therapies are employed. Ezetimibe, which inhibits the Niemann-Pick C1-like 1 (NPC1L1) protein involved in cholesterol absorption, is often combined with statins to further reduce LDL cholesterol levels [84]. Despite their effectiveness, many patients struggle to reach target LDL levels with statins and NPC1L1 inhibitors alone. Additionally, statins may cause muscle-related side effects in some patients, complicating their use [84]. In recent years, non-statin lipid-lowering agents have emerged as new options for managing dyslipidemia. One of the most promising advancements is the development of protein convertase subtilisin/kexin type 9 (PCSK9) inhibitors [85]. PCSK9 is a protein that mediates the degradation of hepatic LDL receptors, which are crucial for clearing LDL cholesterol from the bloodstream [86]. Monoclonal antibodies targeting PCSK9, such as evolocumab and alirocumab, have shown remarkable efficacy in reducing LDL cholesterol levels by 50–60%, surpassing the reductions achievable with NPC1L1 inhibitors [87]. However, the high cost and injection-based delivery of these agents limit their accessibility. To overcome these challenges, innovative approaches including antisense oligonucleotides, genome editing, and vaccines, are being developed, offering potential improvements in durability, more convenient administration, and cost-effectiveness [88].

Bempedoic acid represents a novel addition to lipid-lowering treatment. This agent functions by inhibiting adenosine triphosphate-citrate lyase, an enzyme involved in the cholesterol biosynthesis pathway, positioned upstream of the hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase, the target of statins. Clinical trials have demonstrated that bempedoic acid effectively lowers LDL cholesterol levels, leading to its approval by both the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for

treating hypercholesterolemia [89]. Beyond LDL cholesterol, other apolipoprotein B-containing lipoproteins, like lipoprotein(a) (Lp(a)) and triglyceride-rich lipoproteins, also contribute to cardiovascular risk [90]. Elevated Lp(a) levels, which remain largely unaffected by conventional lipid-lowering therapies, are associated with an increased risk of ASCVD independent of LDL cholesterol levels. Although the novel PCSK9 inhibitor evolocumab can reduce Lp(a) by approximately 20–30%, traditional lipid-lowering drugs have limited impact on Lp(a) levels [91]. A promising new approach involves olpasiran, a small interfering RNA conjugated with acetylgalactosamine that targets hepatic Lp(a) production. Phase 2 trials have shown that olpasiran can reduce Lp(a) levels by over 90%, with further research needed to evaluate its impact on cardiovascular outcomes [92].

Effective and economical agents for lowering triglycerides include fibrates, niacin, and omega-3 fatty acids [93]. These treatments help manage plasma triglyceride levels, which serve as biomarkers for various triglyceride-rich lipoproteins, such as chylomicron remnants, very low-density lipoprotein (VLDL), and intermediate-density lipoprotein (IDL) [94]. Elevated triglycerides are linked to increased atherosclerosis risk. Lipoprotein lipase (LPL), the enzyme responsible for triglyceride breakdown, is critical in this process. Reduced LPL activity or levels can lead to increased triglyceride and triglyceride-rich lipoprotein concentrations [95]. New therapies targeting apolipoprotein C3 and angiopoietin-like protein 3 (ANGPTL3) have proven to be effective in reducing triglyceride levels. For instance, volanesorsen, an antisense oligonucleotide targeting apolipoprotein C3, has been shown to reduce plasma triglyceride levels by approximately 70% [96], while inhibitors of ANGPTL3, such as evinacumab and vupanorsen, have significantly reduced circulating triglycerides and LDL cholesterol [97]. High-density lipoprotein (HDL) cholesterol, rich in apolipoprotein A-I, is traditionally linked to a lower risk of ASCVD due to its anti-inflammatory and anti-atherogenic properties. However, recent evidence suggests that merely increasing HDL cholesterol levels may not improve cardiovascular outcomes and could even raise non-cardiovascular disease risk. This has led to a shift in focus towards enhancing the quality of HDL rather than merely increasing its quantity [98].

Cardiac lipid dysregulation

Cardiac lipid dysregulation encompasses the anomalous processing and accumulation of lipids within the heart, significantly impacting cardiovascular health. This process involves a series of steps, including lipid uptake, fatty acid oxidation, and esterification, all regulated by various proteins and enzymes such as fatty acid transport proteins (FATPs), carnitine palmitoyltransferase 1 (CPT1), and acyl-CoA dehydrogenases [99].

This chronic buildup primarily includes triglycerides, free fatty acids, and ceramides. Such accumulation impairs cellular function by inducing oxidative stress and inflammation, ultimately contributing to cardiac dysfunction and failure [100]. Additionally, alterations in phospholipid metabolism, such as changes in cardiolipin composition, impact mitochondrial function and can exacerbate ischemic injury and cardiomyopathy [101]. Lipid transport mechanisms, such as those involving FATPs and fatty acid-binding proteins (FABPs), can influence the extent of lipid accumulation in cardiomyocytes [102]. Furthermore, lipid synthesis pathways, including those regulated by HMG-CoA reductase and adenosine triphosphate-citrate lyase (ACL), are critical in maintaining lipid balance and mitigating dysregulation [103]. Specific lipid species, like ceramides and altered cardiolipin, are particularly relevant in the context of cardiac disease, as they contribute to fibrosis, impaired function, and increased susceptibility to ischemic events [104].

Diagnosis of lipid associated disorders and diseases

Clinical and laboratory evaluation

The diagnosis of lipid disorders necessitates a comprehensive approach that integrates both clinical evaluation and laboratory testing. Clinicians gather a detailed patient history and perform a thorough physical examination, assessing lifestyle factors like diet, exercise, and alcohol consumption and smoking habits, as well as any family history of lipid disorders or cardiovascular diseases. This evaluation is critical for identifying genetic predispositions, like hypercholesterolemia (FH), and physical signs like xanthomas and corneal arcus, which may indicate severe dyslipidemia. The laboratory assessment commences with a lipid profile, measuring total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG). LDL-C, often referred to as 'bad cholesterol' due to its role in atherogenesis, is a primary focus, whereas HDL-C, known as 'good cholesterol,' offers protective cardiovascular benefits [105]. Elevated triglycerides are also important, indicating potential cardiovascular risk and underlying metabolic issues. Advanced testing, including the measurement of apolipoproteins such as Apolipoprotein B (ApoB) and Apolipoprotein A-I (ApoA-I), provides additional insight into lipid-related risks. ApoB, in particular, offers a superior prediction of cardiovascular risk compared to LDL-C alone. Additionally, the measurement of Lipoprotein(a) [Lp(a)], an independent cardiovascular risk factor, is crucial for individuals with a significant family history of

early heart disease or unexplained cardiovascular events [106].

Genetic testing

Genetic testing is indispensable in the diagnosis of lipid disorders, particularly hereditary conditions like Familial Hypercholesterolemia (FH). FH is characterized by elevated levels of low-density lipoprotein cholesterol (LDL-C), significantly increasing the risk of premature cardiovascular disease. Diagnostic testing for FH typically screens for mutations in three pivotal genes: LDLR, APOB, and PCSK9 [107]. LDLR gene mutations impede the body's capacity to clear LDL cholesterol, while APOB mutations disrupt the binding of LDL particles to receptors. Gain-of-function mutations in PCSK9 exacerbate LDL receptor degradation, thereby further elevating LDL-C levels. Identifying these genetic mutations confirms an FH diagnosis and enables cascade screening of family members, facilitating early intervention and treatment [108].

Beyond monogenic disorders like FH, numerous lipid abnormalities are polygenic, arising from multiple genetic variants [109]. Increased risks of conditions such as hypercholesterolemia, hypertriglyceridemia, or low HDL-C levels can be analyzed by specific single nucleotide polymorphisms (SNPs). Polygenic risk scores, which aggregate the effects of these SNPs, provide a comprehensive risk assessment, especially when integrated with clinical and lifestyle factors [110]. This genetic information is crucial for personalized medicine, as it allows for tailored treatment strategies. For example, individuals with certain genetic profiles may exhibit a more favorable impact to explicit lipid-lowering remedies, such as statins or PCSK9 inhibitors [111]. Additionally, some genetic variants can predict adverse drug reactions, thereby enabling safer and more efficacious treatment choices [112].

Genetic testing also encompasses important considerations related to genetic counseling and ethics. Patients undergoing testing should receive appropriate counseling to understand the implications of their results, including potential psychological impacts and the necessity to inform family members who may also be at risk. Ethical considerations include issues of privacy, informed consent, and the potential for genetic discrimination in employment or insurance, which must be addressed to safeguard patient rights and confidentiality [113].

Emerging biomarkers and techniques for diagnosis

The landscape of lipid disorder diagnostics is continually evolving, with the advent of novel biomarkers and advanced analytical techniques significantly enhancing our grasp of lipid metabolism and cardiovascular risk. Traditional lipid panels encompassing total cholesterol, LDL-C, HDL-C, and triglycerides provide a foundational assessment but fail to capture the intricate complexity of lipid particles. Advanced lipoprotein testing, such as nuclear magnetic resonance (NMR) spectroscopy and ion mobility analysis, offers detailed insights by measuring the size, number, and density of lipoprotein particles [114]. Apolipoproteins, notably ApoB and Lipoprotein(a) [Lp(a)], serve as vital biomarkers; ApoB reflects the total number of atherogenic particles, while high Lp(a) levels are linked to increased cardiovascular risk, especially in conditions like familial hypercholesterolemia (FH) [115]. Inflammatory markers, such as high-sensitivity C-reactive protein (hs-CRP), and assessments of endothelial function, including flow-mediated dilation (FMD), provide additional insights into systemic inflammation and vascular health [116]. Non-invasive imaging techniques, like carotid intima-media thickness (CIMT) measurement and coronary artery calcium (CAC) scoring, are crucial for evaluating atherosclerosis and predicting cardiovascular events [117]. Emerging fields like proteomics and metabolomics are identifying novel biomarkers and pathways in lipid metabolism, offering profound insights into disease mechanisms and potential therapeutic targets [118].

The integration of advanced technologies has revolutionized the ability to monitor emerging biomarkers, ensuring more precise and dynamic tracking of lipid metabolism and cardiovascular risk. Mass spectrometry-based proteomics and metabolomics platforms are increasingly utilized to identify and quantify apolipoproteins, lipid metabolites, and inflammatory mediators with high sensitivity and specificity. For example, tandem mass spectrometry (LC-MS/MS) allows simultaneous measurement of ApoB, ApoA1, and Lipoprotein(a), providing a comprehensive lipid profile in a single assay [119]. Imaging technologies, such as fluorescence-based microscopy and near-infrared spectroscopy (NIRS), are used for the direct visualization of lipid deposition in arterial walls, offering real-time insights into atherosclerotic plaque composition and progression [120]. For systemic biomarkers like hs-CRP, enzyme-linked immunosorbent assays (ELISA) remain a gold standard for quantification in both research and clinical settings [121]. Additionally, microfluidic biosensors and lab-on-a-chip platforms are emerging as portable, rapid, and cost-effective tools for monitoring lipid-related biomarkers in point-of-care settings. These devices integrate multiple detection modalities to assess biomarkers such as ApoB, Lp(a), and inflammatory proteins with minimal sample volume and turnaround time [122]. Furthermore, molecular imaging techniques like PET-CT are being explored for tracking molecular-level changes in lipid and inflammatory pathways, particularly in research scenarios

focusing on drug efficacy and disease progression [122]. Continuous biomarker monitoring is integral to preventive therapy, enabling early detection of lipid abnormalities and timely intervention. Advances in wearable devices and point-of-care testing provide real-time data on markers like LDL-C, Lp(a), and hs-CRP, guiding personalized lifestyle and pharmacological strategies. By integrating such monitoring with predictive analytics, clinicians can proactively mitigate cardiovascular risks, emphasizing a shift from reactive to preventive care [123, 124].

Therapeutic advancements

Advances in treatment of lipid associated disorders

Treating lipid-associated disorders involves a multifaceted approach that extends beyond standard pharmacological therapies to encompass advanced interventions and lifestyle modifications. While medications such as statins, PCSK9 inhibitors, and newer agents like bempedoic acid are pivotal in managing lipid levels, lifestyle changes form the cornerstone of effective treatment [125]. Additionally, regular physical activity—aiming for 150 min of reasonable physical activity per week, not only aids in weight management but also positively influences HDL cholesterol and triglyceride levels [125]. Patient education and adherence to treatment are vital components of successful management. Creating awareness among patients on the significance of medication observance, probable side effects, and lifestyle modifications can improve treatment results. Tools such as mobile health apps provide support for monitoring medication adherence and lifestyle modifications, offering feedback and support to patients [126]. Comorbid conditions such as diabetes and hypertension often accompany lipid disorders and must be managed concurrently. Effective regulation of blood glucose levels in diabetic patients can improve lipid profiles, while managing hypertension helps reduce the cardiovascular risks associated with dyslipidemia (Table 2) [127].

The advent of personalized medicine represents a monumental advancement in lipid disorder treatment [147]. Pharmacogenomic testing enables the tailoring therapies grounded on a person's genetic profile, augmenting treatment efficacy and lessening adverse reactions. Novel therapeutic approaches like RNA-based therapies like inclisiran, target specific RNA molecules to modulate lipid metabolism, offering promising results in reducing LDL cholesterol levels with less frequent dosing [148]. Additionally, gene-editing technologies and antisense oligonucleotides are being explored as potential treatments for genetic lipid disorders, showing the potential to revolutionize current therapeutic paradigms (Table 2) [149]. Integrative approaches, including dietary supplements like incorporating omega-3 fatty acids, plant sterols, and antioxidants, may also support cardiovascular health. However, these supplements should complement rather than replace mainstream medicine and be used under medical surveillance to avoid interactions with prescribed medications [150].

Advances in lipid metabolism and cancer: implications for colon and pancreatic cancers

Significant progress in cancer research has elucidated the intricate interplay between lipid metabolism and tumor development, particularly in colon and pancreatic cancers. Recent technological breakthroughs have enabled researchers to delve deeper into the metabolic signatures and reprogramming that characterize these malignancies, offering new insights into potential therapeutic targets and diagnostic biomarkers. One key area of focus has been the exploration of metabolomic approaches to predict cancer behavior and response to treatment. Metabolomics has developed as a commanding tool in cancer research, allowing for the identification of unique metabolic signatures related to various cancer types, including colon and pancreatic cancers [151].

Cancer cells frequently exhibit a distinct metabolic phenotype, characterized by alterations in lipid metabolism that underpin their rapid proliferation and survival [152]. These metabolic transformations, collectively known as "metabolic reprogramming," empower cancer cells to generate energy, macromolecules, and signaling molecules more efficiently, fueling their uncontrolled growth and invasive capabilities [151–154]. Progress in systematic platforms, such as chromatography and mass spectrometry-based techniques, have eased the analysis of lipid metabolites in cancer cells and tissues. These studies have revealed that colon and pancreatic cancers often display dysregulation in various lipid metabolic pathways, including fatty acid synthesis, lipid oxidation, and cholesterol metabolism [152] For instance, it was reported that elevated levels of specific fatty acids and lipids have been detected in colon and pancreatic cancer samples, suggesting their potential as biomarkers for early detection and disease monitoring [153]. Cancer development and progression of these cancers are aligned with dysregulated enzymes, like fatty acid synthase and acetyl-CoA carboxylase [152, 153, 155].

The metabolic relations between tumor cells and their adjacent microenvironment, including immune cells and stromal cells, have also arisen as a serious factor in cancer progression. These intercellular metabolic communications can significantly influence tumor growth, metastasis, and the response to therapy. Leveraging insights from metabolomic studies, researchers are developing new therapeutic strategies targeting lipid metabolism

Table 2 Lipid management treatment approaches

Treatment Category	Treatment	Mechanism of Action	Indications	Examples	Notes	Reference
Lifestyle Modifications	Dietary Changes	Lowers LDL-C, triglycerides; increases HDL-C and fiber intake	General management of lipid levels	Mediterranean diet, DASH diet	Essential first-line approach; improves lipid profiles significantly	[128]
	Physical Activity	Reduces LDL-C and triglycerides; increases HDL-C	General management, especially for overweight/obesity	150 min of moderate exercise per week	Aerobic exercise is highly recommended for improving cardiovascular health	[129]
	Weight Management	Reduces LDL-C, triglycerides; increases HDL-C	Obesity-related dyslipidemia	Behavioral weight loss programs	Even modest weight loss can lead to substantial improvements in lipid profiles	[130]
	Smoking Cessation	Increases HDL-C; reduces oxidative stress	High cardiovascular risk, improves overall health	Smoking cessation programs	Essential for cardiovascular risk reduction; improves lipid levels and vascular function	[131]
	Alcohol Moderation	Reduces triglycerides; decreases cardiovascular risk	Management of triglyceride levels	Limiting intake to moderate levels	Excessive alcohol intake significantly impacts triglyceride levels and overall health	[132]
Pharmacological Therapies	Statins	Inhibit HMG-CoA reductase; decrease cholesterol synthesis	High LDL-C, atherosclerosis, cardiovascular disease risk	Atorvastatin, Rosuvastatin, Pitavastatin	Most effective first-line therapy; newer statins like rosuvastatin show greater LDL-C reduction and improved safety profiles.	[133]
	Ezetimibe	Blocks cholesterol absorption in the small intestine	High LDL-C, used in combination with statins or alone	Ezetimibe	Enhances LDL-C lowering when combined with statins; effective for statin-intolerant patients.	[134]
	PCSK9 Inhibitors	Prevent degradation of LDL receptors; increase LDL-C clearance	Severe hypercholesterolemia, familial hypercholesterolemia	Alirocumab, Evolocumab	Latest class of lipid-lowering drugs; highly effective for those with severe LDL-C elevations.	[135]
	Fibrates	Activate PPAR-α; increase HDL-C, reduce triglycerides	Hypertriglyceridemia, mixed dyslipidemia	Fenofibrate, Pemafibrate	Newer fibrates like pemafibrate offer improved efficacy and safety over older agents.	[136]
	Niacin	Inhibits hepatic VLDL secretion; raises HDL-C, lowers triglycerides	Low HDL-C, high triglycerides	Extended-release niacin	New formulations reduce flushing; effectiveness in raising HDL-C and lowering triglycerides can be significant but may be limited by side effects.	[137]
	Bile Acid Sequestrants	Bind bile acids; increase hepatic cholesterol uptake	High LDL-C, often used with statins for additive effect	Colesevelam, Cholestyramine	Newer agents like colesevelam have better tolerability; effective in lowering LDL-C and improving glycemic control.	[138]

Table 2 (continued)

Treatment Category	Treatment	Mechanism of Action	Indications	Examples	Notes	Reference
	Omega-3 Fatty Acids	Reduce hepatic triglyceride production; anti-inflammatory effects	Severe hypertriglyceridemia	Icosapent ethyl, Omega-3 carboxylic acids	Prescription omega-3s such as icosapent ethyl show significant cardiovascular risk reduction and triglyceride lowering.	[139]
	Bempedoic Acid	Inhibits ATP-citrate lyase; reduces cholesterol synthesis	High LDL-C, especially when used with statins or in statin-intolerant patients	Bempedoic acid	New agent that offers LDL-C reduction; can be used in conjunction with other therapies.	[140]
Advanced Interventions	Lipoprotein Apheresis	Removes LDL and other lipoproteins from the blood	Severe FH, refractory to pharmacotherapy	-	Used for patients with extreme dyslipidemia; requires regular treatments to maintain LDL-C reductions.	[141]
	Gene Therapy	Corrects genetic mutations affecting lipid metabolism	Familial hypercholesterolemia (under research)	-	Promising experimental approach for addressing genetic causes of dyslipidemia; ongoing research into efficacy and safety.	[142]
	RNA-based Therapies	Target specific RNA molecules to modulate lipid metabolism	High LDL-C, specific genetic profiles	Inclisiran, other small interfering RNAs	Inclisiran targets PCSK9 mRNA to lower LDL-C; shows promise for long-term LDL-C reduction with biannual dosing.	[143]
	Monoclonal Antibodies	Target specific proteins involved in lipid metabolism	Severe hypercholesterolemia, mixed dyslipidemia	Evinacumab (in clinical trials)	Targets ANGPTL3 to lower LDL-C and triglycerides; novel approach with potential for high-risk populations.	[144]
	Cholesterol Ester Transfer Protein (CETP) Inhibitors	Increase HDL-C by preventing cholesterol transfer from HDL to LDL	Low HDL-C, atherosclerosis	Anacetrapib (development phase)	CETP inhibitors are in development; aim to raise HDL-C and reduce cardiovascular risk.	[145]
Regular Monitoring and Follow-Up	Monitoring & Adjustments	Assesses treatment response and side effects; adjusts therapy	Ongoing management of lipid disorders	Routine lipid panels, advanced imaging	Essential for optimizing treatment efficacy and adapting to changes in lipid levels	[146]

in colon and pancreatic cancers. These approaches aim to disrupt the metabolic pathways that support tumor growth. One promising strategy involves targeting fatty acid uptake [152]. Free fatty acids can diffuse across the cell membrane, facilitated by proteins like fatty acid binding proteins (FABPs) and fatty acid transport proteins (FATPs). Inhibiting CD36-mediated fatty acid uptake, a key process in cancer metastasis, has emerged as a promising cancer therapy. Studies have shown that CD36 has been linked to metastasis of various cancer types, including head and neck, ovarian, prostate, breast, lung, renal, and gastric cancers, as well as glioblastoma and leukemia. Notably, it has been demonstrated that CD36 plays a crucial role in breast cancer metastasis in mice fed a high-fat diet, and that the systemic deletion of CD36 following tumor development can inhibit metastasis. Furthermore, CD36 has been linked to resistance to HER2-targeted therapy in breast cancer [154].

The expanding understanding of lipid metabolic reprogramming in colon and pancreatic cancers is unveiling new avenues for cancer research and treatment. The identification of specific metabolic signatures and the elucidation of the intricate interplay between tumor cells and their microenvironment hold promise for developing more effective diagnostic tools and personalized therapeutic approaches targeting lipid metabolism in these challenging malignancies [151–153]. Currently, there is an ongoing effort to develop a humanized CD36-inhibitory antibody for potential clinical use, which could pave the way for novel targeted therapies by disrupting the metabolic pathways that support tumor growth. Advancements in understanding of lipid uptake and its significant contribution to the pathogenesis of colon and pancreatic cancers have opened new avenues for cancer diagnosis, prognosis, and targeted therapy. The incorporation of cutting-edge metabolomics technologies with other-omics approaches, like that of genomics and transcriptomics, has the potential to unravel the complex metabolic landscape of these cancers, ultimately leading to more personalized and effective treatment strategies [151–153].

Challenges

Lipid dysregulation is implicated in a wide array of health conditions, including cancer, metabolic disorders, diabetes, cardiovascular diseases, and neurodegenerative diseases [156]. In cancer, reprogrammed lipid metabolism n is intricately linked to oncogenic signals, metastasis, and therapeutic resistance [151–157]. Targeting transcription factors involved in lipid rewiring offers a promising strategy for cancer therapy. Metabolic disorders such as brain lipid dysregulation, abnormal lipid profiles and lipotoxicity are major contributors to disease onset. Lipid dysregulation in the brain is closely related to conditions like Alzheimer's disease, Parkinson's disease, and frontotemporal dementia [158]. Abnormal lipid profiles contribute to insulin resistance, a defining feature of type II diabetes. Excessive lipids can cause lipotoxicity, impairing pancreatic beta-cell function. Given that both CVD and lipid/metabolic disorders predominantly affect aging populations, balancing lipid management with cancer treatment becomes increasingly crucial [159]. Cancer cell epigenetics also play a role in disrupting lipid metabolism, affecting membrane synthesis, energy production, and oxidative stress response. In summary, a comprehensive understanding of lipid dysregulation and developing targeted therapies remains essential for managing these complex diseases.

Complexity of lipid metabolism

Lipid metabolism encompasses the production, degradation, utilization of various lipid classes, including triglycerides, phospholipids, sphingolipids, and sterols. Each class performs distinct cellular functions, such as energy conservation, membrane integrity, and signaling. Triglycerides serve as energy reservoirs; phospholipids are crucial for cellular membrane synthesis and signaling pathways transduction. Sphingolipids are involved in apoptosis and cell growth, and sterols like cholesterol are vital for membrane fluidity and hormone synthesis [160]. The regulation of lipid metabolism is highly dynamic, involving enzymes, transport proteins, and signaling molecules. Key enzymes like acetyl-CoA carboxylase and fatty acid synthase are regulated by hormonal signals and intracellular metabolites. Transporters, including the ATP-binding cassette (ABC) family, facilitate lipid distribution. The mechanistic target of rapamycin (mTOR) pathway, which coordinates metabolic and signaling networks, is also pivotal in lipid metabolism [161]. This metabolic system is interconnected with carbohydrate and protein metabolism, with acetyl-CoA serving as a central intermediate. Dysregulation of lipid metabolism can result in metabolic diseases like obesity, type II diabetes, and cardiovascular diseases [18]. Studying this complex system is challenging due to the diversity of lipid species and the need for advanced analytical techniques like lipidomics. Understanding the intricacies of lipid metabolism is essential for developing targeted therapies for metabolic diseases.

Pathophysiological roles of lipids

Understanding the pathophysiological roles of lipids is inherently complex due to their diverse functions in cellular processes. Dysregulation of these lipids can lead to a wide range of pathologies. One significant challenge is the dual role of lipids as both structural components and

signaling molecules. For instance, disruptions in phospholipid and sphingolipid metabolism can impair cellular communication and induce apoptosis, contributing to conditions like metabolic and neurodegenerative diseases [162]. Triglycerides, important for energy storage, can lead to metabolic disorders if excessively accumulated, complicating the understanding of their regulation [163]. In cardiovascular diseases, the complex roles of lipoprotein, such as LDL in atherosclerosis and the nuanced protective role of HDL, pose formidable challenges for the effective management of dyslipidemias [164]. In neurodegenerative diseases, lipid dysregulation, particularly involving sphingolipids and cholesterol, contributes to disease pathology through various mechanisms, including those summarized in Fig. 3. Technical challenges in lipidomics and the need for precise analytical techniques further complicate the study of lipid dysregulation [165].

Genetic and environmental factors

The interaction between genetic predisposition and ecological aspects significantly augments the complexity of lipid dysregulation. Genetic predispositions, such as mutations in genes integral to lipid metabolism, can lead to conditions like familial hypercholesterolemia, wherein elevated LDL cholesterol level increases cardiovascular risk [105]. The polygenic nature of numerous lipid disorders complicates the elucidation of specific genetic etiologies, necessitating comprehensive genetic analysis. Additionally, gene-environment interactions profoundly influence lipid metabolism, with environmental factors like diet and physical activity either exacerbating or mitigating genetic risks [166]. Unhealthy eating habits, including the ingestion of saturated and trans fats, can elevate LDL cholesterol levels, while physical inactivity is concomitantly associated with obesity and adverse lipid profiles [167]. These factors vary greatly among individuals and populations, influenced by socioeconomic and cultural contexts, thereby complicating the development of uniform guidelines and interventions. The burgeoning prevalence of lifestyle-related issues, such as obesity and inactive behavior, exacerbates the challenge of managing lipid dysregulation on a population level [168].

The interaction between genetic and environmental factors poses additional challenges, as individuals with genetic susceptibilities may experience amplified effects from adverse environmental conditions. Conversely, salutary lifestyle choices can occasionally counteract genetic risks. Understanding these complex interactions is paramount for personalized medicine, which aspires to tailor prevention and treatment strategies based on individual risk profiles. However, this endeavor necessitates extensive research and advanced analytical tools, rendering it a resource-intensive pursuit. Addressing these challenges is critical for the development of effective interventions and enhancement of overall metabolic health [168].

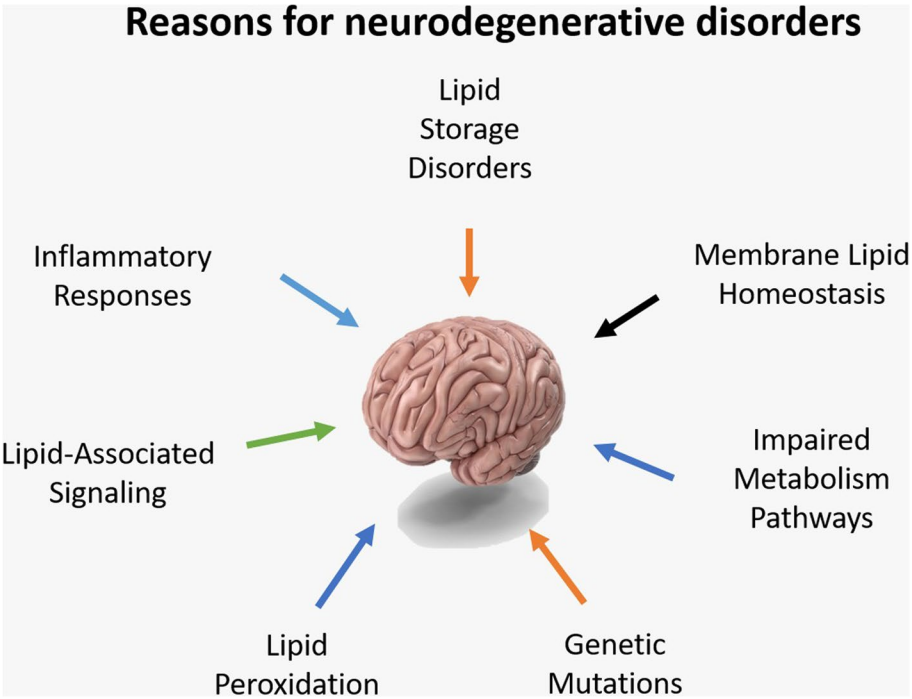

Fig. 3 Mechanisms contributing to neurodegenerative disorders related to lipid dysregulation

Diagnostic and therapeutic challenges

Lipid dysregulation presents formidable challenges in both diagnosis and treatment due to the complicated nature of lipid metabolism and the various roles lipids serve in the body. Standard lipid panels measuring total cholesterol, LDL, HDL, and triglycerides do not fully capture the nuances of lipid abnormalities [169]. For example, small, dense LDL particles are more atherogenic than bigger counterparts, yet this is not typically assessed. Additionally, while HDL is generally considered protective, its functionality can vary, and dysfunctional HDL may contribute to cardiovascular risk. Advanced testing methods like NMR spectroscopy and lipidomics can provide more detailed insights but are prohibitively expensive and not widely accessible [170, 171].

Therapeutically, managing lipid disorders often begins with lifestyle alterations, such as changes in diet, increased exercise and so on. However, patient adherence and variability in response pose significant challenges. Pharmacological treatments, such as statins, are commonly employed to lower LDL cholesterol, but may not be universally effective and can have side effects. Newer drugs, like PCSK9 inhibitors, offer more potent LDL reduction but are associated with high costs and require regular administration [172]. Raising HDL levels and improving HDL functionality remain therapeutic challenges, as some treatments have not consistently shown cardiovascular benefits. Additionally, addressing secondary causes of dyslipidemia, such as diabetes or hypothyroidism, requires a comprehensive treatment approach [173]. The imperative for personalized medicine is evident, as genetic and ecological aspects profoundly influence lipid metabolism and patient responses to therapies [173]. Overcoming these diagnostic and therapeutic challenges is crucial for better managing lipid-related diseases and improving patient outcomes.

Conclusion

The dysregulation of lipid metabolism is a major factor in the development of numerous ailments, including cardiovascular diseases (CVD), metabolic disorders, and neurodegenerative conditions. This analysis in the review culminates the intricate ways of lipid metabolism, highlighting the role of triglycerides, phospholipids, sphingolipids, and cholesterol in sustaining cellular function and maintaining systemic homeostasis. Perturbation in these processes not only precipitates prevalent conditions like dyslipidemia and atherosclerosis, but also contribute to more multifaceted diseases like Alzheimer's disease, Parkinson's disease, and certain malignancies.

The therapeutic landscape for lipid-related disorders has evolved significantly, with the advent of mediators such as PCSK9 inhibitors, bempedoic acid, and antisense oligonucleotides targeting apolipoprotein C3 and Lp(a). These therapies represent a substantial advancement over traditional treatments, offering superior efficacy in lowering lipoprotein cholesterol (LDL-C) levels and addressing other lipid abnormalities. However, the exorbitant costs and limited accessibility of these advanced therapies pose ongoing challenges, particularly in resource-limited settings. Moreover, the reliance on injection-based delivery for some of these treatments raises concerns regarding patient adherence and long-term management.

Despite the advancements in pharmacotherapy, lifestyle modifications remain the cornerstone of managing lipid disorders. Diet, physical activity, and behavioral interventions are essential components of a comprehensive treatment strategy, particularly given the polygenic nature of many lipid disorders. The integration of personalized medicine, guided by genetic testing and polygenic risk scores, offers the potential to tailor treatment strategies more effectively, enhancing both the efficacy and safety of interventions. Pharmacogenomics and emerging technologies like RNA-based therapies and gene editing further expand the therapeutic arsenal, allowing for more precise targeting of lipid metabolism pathways.

The advent of lipidomics and advanced diagnostic techniques, including nuclear magnetic resonance (NMR) spectroscopy and metabolomics, is revolutionizing our understanding of lipid metabolism. These technologies provide a more nuanced understanding of lipoprotein function, offering new potential biomarkers and treatment targets. As these technologies advance, they hold the promise of improving diagnostic accuracy, enabling earlier detection of lipid-related disorders, and refining treatment strategies to better address individual patient needs. Nevertheless, significant challenges remain. The intersection of lipid metabolism with other physiological systems—such as insulin signaling, inflammatory pathways, and mitochondrial function, add complexity to both the understanding and treatment of lipid disorders. Additionally, the role of environmental factors, including diet, lifestyle, and exposure to toxins, in modulating lipid metabolism cannot be overlooked, highlighting the necessity for a comprehensive treatment approach that considers the full spectrum of genetic, environmental, and lifestyle influences. Future research should focus on elucidating the molecular mechanisms linking lipid metabolism with other critical pathways, such as inflammation and mitochondrial function, to identify novel therapeutic targets. Investigating the interplay between genetic predisposition and environmental influences can further refine risk stratification and therapeutic interventions. Additionally, clinical trials assessing the long-term efficacy and safety of emerging RNA-based therapies and gene-editing approaches are crucial. Expanding access

to advanced diagnostics and treatments, particularly in resource-limited settings, remains a pressing need to ensure equitable healthcare delivery worldwide.

In conclusion, addressing the multifaceted challenges of lipid dysregulation necessitates an integrative approach that combines advanced diagnostic tools, novel therapeutic agents, and personalized treatment strategies. As research progresses, it is imperative that these insights are seamlessly translated into clinical practice, ensuring that the benefits of new therapies are accessible to all patients. By embracing a comprehensive and personalized approach to the management of lipid disorders, we can significantly improve outcomes for a wide array of diseases and move closer to achieving optimal cardiovascular and metabolic health on a global scale.

Abbreviations

ABC	ATP-binding cassette
ACL	Adenosine triphosphate-citrate lyase
ACS	Acute coronary syndrome
AMPK	AMP-activated protein kinase
ANGPTL3	Angiopoietin-like protein 3
ApoA-I	Apolipoprotein A-I
ApoB	Apolipoprotein B
ApoB	Apolipoprotein B
ApoC3	Apolipoprotein C3
ASCVD	Atherosclerotic cardiovascular disease
BBB	Blood-brain barrier
BDNF	Brain-derived neurotrophic factor
CAC	Coronary artery calcium
CIMT	Carotid intima-media thickness
CNS	Central nervous system
CPT1	Carnitine palmitoyltransferase 1
CVD	Cardiovascular diseases
ELISA	Enzyme-linked immunosorbent assay
EMA	European medicines agency
FABP	Fatty acid binding protein
FABPs	Fatty acid binding proteins
FATPs	Fatty acid transport protein
FDA	Food and drug administration
FH	Familial hypercholesterolemia
FTO	Fat mass and obesity-associated gene
HDL	High-density lipoprotein
HDL-C	High-density lipoprotein cholesterol
HFD	High-fat diet
HMG-CoA	Hydroxymethylglutaryl coenzyme A
hs-CRP	High-sensitivity C-reactive protein
IDL	Intermediate-density lipoprotein
IL	Interleukin
LC-MS/MS	Liquid chromatography-tandem mass spectrometry
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein cholesterol
LDLR	Low-density lipoprotein receptor
Lp(a)	Lipoprotein(a)
LPL	Lipoprotein lipase
LPS	Lipopolysaccharide
mTOR	Mechanistic target of rapamycin
NF-κB	Nuclear factor kappa B
NGF	Nerve growth factor
NIRS	Near-infrared spectroscopy
NK	Natural killer cells
NMR	Nuclear magnetic resonance
NPC1L1	Niemann-Pick C1-like 1
NPD	Niemann-Pick disease
PCSK9	Proprotein convertase subtilisin/kexin type 9
PET-CT	Positron emission tomography-computed tomography
PPARs	Peroxisome proliferator-activated receptors
ROS	Reactive oxygen species
SIRT1	Sirtuin 1
SNPs	Single nucleotide polymorphisms
TC	Total cholesterol
TG	Triglycerides
TLR4	Toll-like receptor 4
TNF	Tumor necrosis factor
Treg	Regulatory T cells
Trkβ	Tropomyosin receptor kinase B
VLDL	Very low-density lipoprotein
WAT	White adipose tissue

Authors' contributions

TCD, CJ and XDB conceived the idea and prepare the outline and first draft of the manuscript; TCD, XF, CKB, PCS wrote the manuscript; TCD, CKB, PCS, RS prepared figures/tables for the manuscript; TCD, RS, CJ and XDB review the manuscript; All the authors have read and approved the submission of the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not Applicable.

Competing interests

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