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REVIEW

Lipotoxicity: A New Perspective in Type 2 Diabetes Mellitus

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Abstract: Type 2 diabetes mellitus is a non-communicable metabolic disorder characterized by insulin resistance (IR) associated with defects in insulin production and secretion. Recent studies have shown that lipotoxicity, which is characterized by the abnormal accumulation of lipids in non-adipose tissues, leads to bodily dysfunction and metabolic disorders, thereby promoting the progression of T2DM. This process is mediated by the induction of endoplasmic reticulum (ER) stress, oxidative stress (OS), mitochondrial dysfunction, and inflammatory responses in pancreatic β-cells, ultimately leading to the activation of apoptosis pathways, which results in β-cell dysfunction and cell death. Furthermore, lipotoxicity interferes with insulin signaling pathways, which worsens IR. Current clinical approaches aimed at mitigating lipotoxicity-induced IR and β-cell dysfunction include the use of metformin, glucagon-like peptide-1 analogs, thiazolidinediones, and molecular chaperones, in addition to interventions such as caloric restriction and physical activity, which reduce fat accumulation in the pancreas and enhance β-cell function. Investigating the interplay between lipotoxicity and T2DM is essential for understanding the underlying disease mechanisms and providing new insights into prevention and therapeutic strategies. This review offers a comprehensive analysis of the mechanisms underlying lipotoxicity in T2DM, highlighting how these insights may drive future research and inform the development of novel treatment approaches.

Keywords: type 2 diabetes mellitus, adipose tissue, lipotoxicity, insulin resistance

Introduction

Type 2 diabetes mellitus (T2DM) is a non-communicable metabolic disorder characterized by insulin resistance (IR) associated with defects in insulin production and secretion. According to recent data from the International Diabetes Federation (IDF), approximately 537 million adults worldwide had diabetes in 2021, with T2DM representing nearly 90% of all cases. Projections indicate that this figure will rise to 783 million by 2045.[1,2] This growing prevalence has placed a significant economic burden on healthcare systems, societies, and families, emerging as a critical public health challenge that warrants immediate attention. However, the precise mechanisms underlying T2DM remain incompletely understood.

The pathophysiological mechanism of T2DM is primarily driven by IR and pancreatic β-cell dysfunction.[3] Extensive research demonstrated a strong association between obesity and T2DM, with obese individuals exhibiting marked defects in insulin secretion. As obesity progresses, a further decline in insulin secretion is observed, underscoring the close relationship between these two conditions.[4,5] Obesity is characterized by an imbalance between white adipose tissue (WAT) and brown adipose tissue (BAT).[6] White adipose tissue serves as a critical energy reservoir. In individuals with obesity, WAT often becomes highly dysfunctional, resulting in adipocyte hypertrophy, visceral obesity, and ectopic fat deposition,[7] which contribute to the development of T2DM. This suggests a potentially unanticipated function of adipose tissue in the development of T2DM. Previous research has revolutionized the understanding of adipose tissue, shifting its perception

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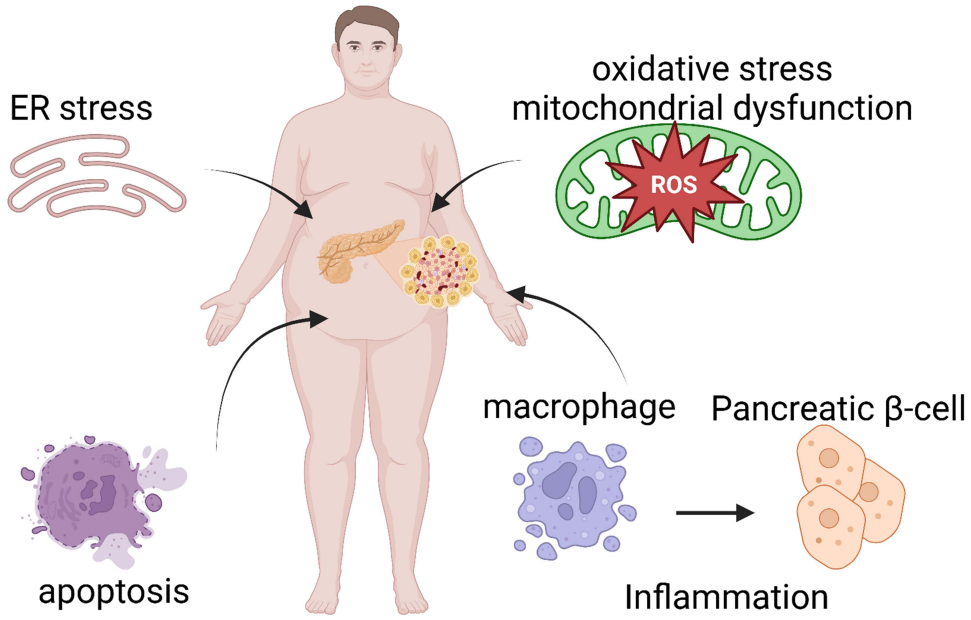
Graphical Abstract



from a mere passive energy reservoir to that of an active "endocrine organ".[8] Hypertrophic adipocytes, macrophage infiltration, impaired insulin signaling, and insulin resistance contribute to the secretion of inflammatory adipokines and elevated levels of free fatty acids (FFAs) within adipose tissue. This cascade of events can ultimately result in ectopic fat accumulation and lipid-induced toxicity in vital organs such as the heart, kidney, liver, and pancreas, thereby significantly compromising their normal physiological functions.[9–11] Lipotoxicity is marked by the abnormal accumulation of lipids in non-adipose tissues, which results in functional impairment and metabolic disturbances.[11] Specifically, the aberrant accumulation of lipid metabolites, such as FFA, can induce lipotoxicity, thereby impairing β-cell function and accelerating the progression of T2DM.[12] Lytrivi outlined that the molecular pathways implicated in lipotoxicity encompass endoplasmic reticulum (ER) stress, oxidative stress (OS), mitochondrial dysfunction, impaired autophagy, and inflammation, with complex crosstalk observed between these pathways, which may drive the progression of diabetes.[13] FFA demonstrated to exert lipotoxic effects on cells in models of obesity-associated diabetes.[14,15] Through laser capture microdissection and microarray analysis of islets obtained from 10 non-diabetic and 10 T2DM donors, Esteve identified that elevated levels of saturated FFAs, particularly palmitic acid, induce lipid toxicity. This subsequently triggers ER stress, OS, and inflammatory responses, all of which impair pancreatic beta cell function and exacerbate hyperglycemia.[16] These studies collectively indicate an inherent association between lipid toxicity and T2DM.

Consequently, this investigation seeks to examine the impact of lipotoxicity on T2DM, with the goal of offering novel insights into the clinical management and therapeutic approaches to the condition.

Adipocyte Function and Lipotoxicity Development

Adipocytes: A Dynamic and Complex Network

Adipose tissue is a complex and heterogeneous structure consisting of various cell types responsible for the storage and release of lipids and fatty acids (FAs) in response to nutrient intake.[17] In addition to its role in energy storage and the secretion of bioactive molecules, adipose tissue functions as a responsive network that detects and reacts to both internal and external environmental signals. Under normal physiological conditions, adipose tissue demonstrates a high degree of insulin sensitivity, with even minimal concentrations of insulin being sufficient to inhibit lipolysis. Furthermore, adipose tissue produces factors like adiponectin and branched fatty acid esters of hydroxy fatty acids that enhance insulin sensitivity.[18] However, in the

context of T2DM, adipocytes undergo functional changes, secreting insulin-resistant molecules like retinol-binding protein 4, tumor necrosis factor α, interleukin-6, and interleukin-1β (IL-1β). These molecules not only promote lipolysis but also induce systemic inflammation, contributing to the development of IR.[8] As a result of this resistance, the breakdown or hydrolysis of triglycerides (TG) is impaired, diminishing the inhibitory effect of insulin on lipolysis and leading to the increased release of FFA and glycerol. Excessive lipid accumulation occurs not only within adipose tissue but also in other tissues, where it is converted into very-low-density lipoprotein TG and secreted by the liver, further contributing to dyslipidemia associated with T2DM.[19] In conclusion, adipose tissue functions as a dynamic and intricate network, where abnormal lipid accumulation serves a pivotal function in the onset of IR.

Lipotoxicity: Abnormal Accumulation of Lipids

Under physiological conditions, FFAs, as intermediates in lipid metabolism, contribute 5% to 10% to the total serum fatty acid pool. However, when FFA levels exceed the oxidative capacity, the excess is converted back into TG within various tissues, leading to abnormal lipid accumulation and the onset of metabolic disorders. In patients with T2DM, lipid deposition in the pancreas can induce β-cell apoptosis and disrupt insulin secretion. In skeletal muscle, lipid accumulation impairs glucose uptake, while in the liver, it causes cellular stress, disrupting glucose utilization, enhancing gluconeogenesis, and potentially resulting in hepatocyte death. The liver, a central site for lipid synthesis, regulates its lipid metabolism through diverse transcription factors and nuclear receptors. Sterol regulatory element-binding proteins (SREBPs), which are membrane-bound transcription factors localized in the ER, mediate hepatic de novo lipogenesis[20,21] by forming complexes with the cholesterol sensor SCAP. When cellular cholesterol levels surpass certain thresholds, the SCAP/SREBP complex interacts with insulin-induced genes (Insigs) and remains sequestered in the ER.[22] When cholesterol concentrations fall below these thresholds, the SCAP/SREBP complex dissociates from Insigs and translocates to the Golgi apparatus. Here, SREBPs undergoes sequential cleavage by the proteases S1P and S2P, resulting in the release of nuclear SREBPs (nSREBPs). These nSREBPs then translocate to the nucleus, where they bind to sterol regulatory elements (SREs) within the promoters or enhancers of target genes, thereby initiating transcription and translation processes that promote lipid synthesis. Mammalian cells express three isoforms of SREBPs: SREBP-1a, SREBP-1c, and SREBP-2. SREBP-2 predominantly regulates the expression of cholesterol synthesis genes, while SREBP-1c, the main SREBP-1 isoform in the liver, controls the expression of genes responsible for fatty acid and triglyceride synthesis.[21] Horton suggested that the overexpression of hepatic nSREBP-1c prevented the reduction in lipogenic mRNA expression following a decrease in plasma insulin levels.[23] Conversely, in SCAP gene knockout mice, which lack all nSREBP isoforms, or in mice deficient in hepatic nSREBP-1c or both SREBP-1 isoforms, insulin-induced lipogenic gene expression was markedly reduced.[24,25] This suggests that SREBPs-mediated hepatic de novo lipogenesis is closely related to insulin (Figure 1).

Ongoing research has revealed that lipotoxicity represents a multifaceted network involving a range of signaling pathways and molecular mechanisms. Heydemann highlighted that lipotoxicity is intricately linked to the initiation and progression of T2DM, with a high-fat diet causing IR and hyperglycemia in mice, subsequently resulting in disturbances in lipid metabolism and the emergence of lipotoxicity.[26] The abnormal accumulation of lipids has been proven to impact pancreatic β-cell function through several mechanisms. First, lipotoxicity induces OS, leading to the production of elevated levels of ROS and contributing to dysfunction in pancreatic islets. Second, lipotoxicity can stimulate inflammatory responses, releasing pro-inflammatory cytokines such as TNF-α and IL-6, which further aggravate IR.[27] Moreover, lipotoxicity has been suggested to provoke ER stress. Lytrivi demonstrated that palmitic acid disrupts protein trafficking from the ER to the Golgi apparatus, resulting in the accumulation of unfolded or misfolded proteins, which activate ER stress signaling pathways and promote pancreatic β-cell apoptosis.[13]

In conclusion, the abnormal accumulation of lipids constitutes a fundamental feature of lipotoxicity. By inducing OS, triggering inflammatory responses, and activating ER stress, lipotoxicity compromises pancreatic β-cell function and facilitates the onset and progression of T2DM.

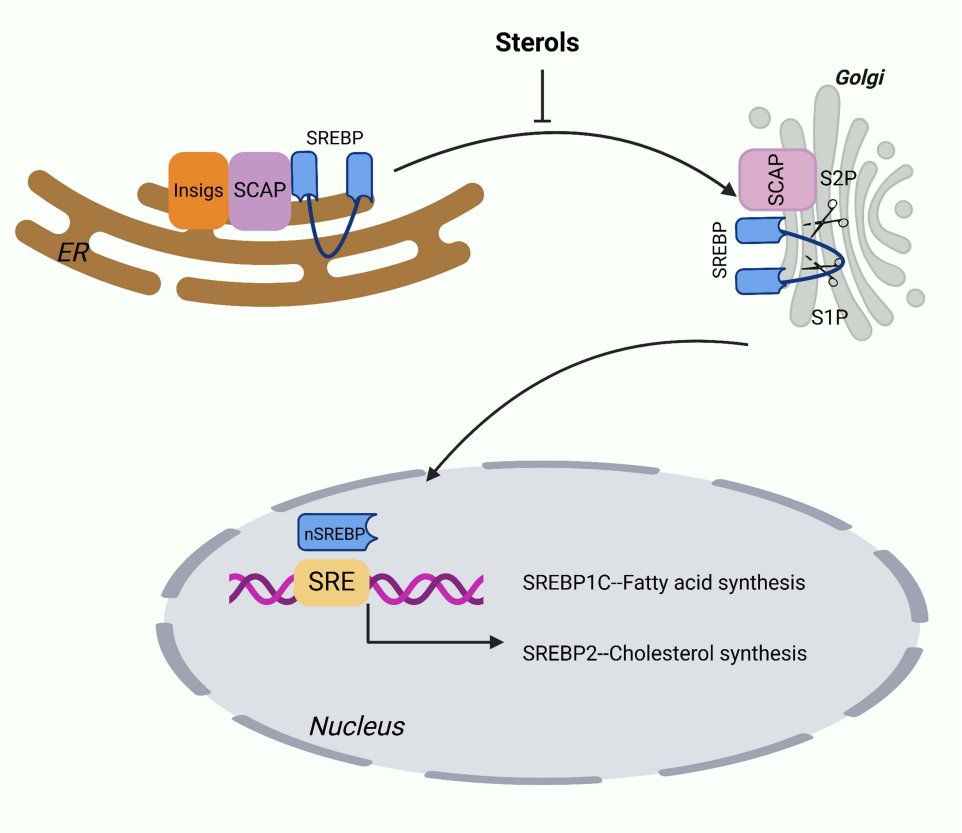


Figure 1 SREBP mediate hepatic de novo lipogenesis. When cholesterol levels exceed a certain threshold concentration, the SCAP/SREBP complex binds to the insulin-inducible gene Insigs and remains in the ER. Conversely, when cholesterol levels fall below this threshold, the SCAP/SREBP complex is released from Insigs and translocates from the ER to the Golgi apparatus. There, SREBP is sequentially cleaved by the proteases S1P and S2P, resulting in the release of nSREBPs, which are then translocated into the nucleus to interact with target gene promoters and enhancers. The SREs of the subunit bind to initiate transcription and translation. SREBP-1c primarily regulates the expression of fatty acid synthesis genes, while SREBP-2 mainly governs the expression of cholesterol synthesis genes. Created in BioRender. Wu, Y (2024) https://BioRender.com/o54q509.

Lipotoxicity Contributes to the Development and Progression of T2DM

Lipotoxicity Activates ER Stress

The ER is an organelle responsible for maintaining protein homeostasis, often referred to as "proteostasis", and ensuring quality control of proteins. Accumulation of misfolded or unfolded proteins within the ER disrupts this homeostasis, thereby triggering the ER stress response.[28] This process is initiated through the activation of three distinct signaling pathways: protein kinase RNA-like ER kinase (PERK), activating transcription factor-6 (ATF6), and inositol-requiring enzyme-1 (IRE1). It has been demonstrated that lipotoxicity-induced ER stress serves a pivotal function in the dysfunction and apoptosis of pancreatic β-cells.[29] Biden proposed that excess FAs disrupt the balance between protein folding and insulin production, thereby triggering the UPR and inducing ER stress.[30] Activation of the UPR promotes cell apoptosis by increasing the level of C/EBP homologous protein (CHOP). The suppression of ER stress could potentially prevent β-cell dysfunction caused by lipotoxicity. ATF6 functions as a transcription factor anchored to the ER membrane. In response to the accumulation of unfolded or misfolded proteins within the ER, the CD1 domain located at the C-terminus detects this stress, triggering the translocation of ATF6 from the ER to the Golgi apparatus.[31] At the Golgi, ATF6 is subjected to sequential proteolytic processing by site-1 protease (S1P) and site-2 protease (S2P).[32,33] This cleavage event facilitates the nuclear translocation of the N-terminal leucine zipper transcription factor domain, which subsequently initiates the transcription of chaperone proteins and enzymes critical for protein folding.[34,35] Consequently, ATF6 is classified as a transcription factor activated in response to ER stress. Studies have indicated that ATF6-knockout mice did not exhibit β-cell functional impairment under normal dietary conditions; however, they showed severe ER stress and reduced insulin levels when subjected to a high-fat diet.[36] Conversely, Xuqing found that overexpression of

ATF6 in the mouse liver promoted hepatic fatty acid oxidation and mitigated IR induced by a high-fat diet.[37] Zeng clarified the mechanism linking ATF6 to lipotoxicity. Using chromatin immunoprecipitation assays, they found that ATF6 (N) forms a complex with SREBP2 (N) at the SRE site, inhibiting SREBP2 (N)'s lipogenic activity in hepatocytes.[38] This indicates that ATF6 may alleviate lipotoxic damage by reducing hepatic lipogenesis. Additionally, Parks observed that lipotoxicity also influences the expression of protein arginine methyltransferase 1, thereby promoting PERK phosphorylation and facilitating ATF6 dissociation.[39] These findings suggest that lipotoxicity contributes to β-cell dysfunction by activating ER stress, particularly through the modulation of ATF6 activity.

PERK serves a pivotal function in the impairment of insulin secretion and β-cell failure, being expressed across various tissues.[40] Mutations in the PERK gene are linked to the development of Wolcott-Rallison syndrome, a condition characterized by defective insulin secretion and β-cell dysfunction. Notably, Zhang demonstrated that modulation of the PERK-ATF4-CHOP signaling pathway in the liver can mitigate ER stress and reverse lipotoxicity-induced IR.[41] PERK activation occurs via dimerization following dissociation from the heavy chain binding protein during ER stress, which subsequently leads to the phosphorylation of eukaryotic translation initiation factor α (eIF2α).[42] This results in translational arrest and a decrease in the synthesis of new proteins in the ER while simultaneously promoting the selective translation of activating transcription factor 4 (ATF4) and its downstream effector, CHOP.[33] ATF4 induces the expression of antioxidant stress response genes and affects β-cell function.

Furthermore, Wang reported that IRE1α is an atypical ER-resident transmembrane protein.[43] As a ribonuclease, IRE1α mediates the splicing of the mRNA of the transcription factor X-box binding protein 1 (XBP1), resulting in the upregulation of several gene sets, including those encoding ER chaperones (GRP78), ER-associated degradation regulatory genes (EDEM1), and pro-apoptotic transcription factors such as CHOP.[44] Moreover, IRE1α interacts with tumor necrosis factor receptor-associated factor 2 (TRAF2), which can activate apoptosis signal-regulating kinase 1 (ASK1), triggering the JNK-mediated pro-apoptotic pathway.[45] Consequently, lipotoxicity can activate IRE1α, leading to the activation of the JNK and CHOP pathways, which ultimately induce pancreatic β-cell apoptosis. Evidence has shown that CHOP expression is induced by ER stress inducers, and CHOP-deficient mice develop without significant defects. Nevertheless, cells from these mice exhibit resistance to ER stress-induced apoptosis,[46] suggesting that CHOP is essential for the apoptotic response to ER stress. CHOP enhances GADD34 expression, which functions as a stress-activated suppressor of additional C/EBP protein family members.[47,48] GADD34 forms a complex with protein phosphatase 1, leading to the dephosphorylation of eIF2α and establishing a negative feedback loop[49] (Figure 2).

In conclusion, lipotoxicity initiates three distinct signaling pathways related to ER stress, which collectively contribute to the development of IR and the dysfunction of pancreatic β-cells.

Lipotoxicity Activates OS and Mitochondrial Dysfunction in Pancreatic β-Cells

OS arises from a disruption in the balance between ROS generation and the antioxidative capacity of the cell.[50] Under normal physiological conditions, ROS are implicated in diverse essential cellular processes. However, when ROS levels become excessive, they compromise β-cell functionality. Chronic nutrient overload, particularly due to elevated levels of FFAs, results in ROS accumulation that surpasses the cell's ability to clear them, thereby inducing OS.[51] FFA induces the production of ROS through multiple pathways. First, excessive FFA can enhance the activity of mitochondrial β-oxidation, resulting in an overload of the electron transport chain (ETC) and an increased generation of superoxide anions, which subsequently elevates ROS levels. Additionally, FFA can stimulate ROS production by activating NADPH oxidase (NOX). Specifically, palmitic acid can upregulate the expression of NOX2 through the activation of protein kinase Cα (PKCα), thereby further increasing ROS production.[52] It is important to note that the degree of saturation and chain length of fatty acids significantly influence their capacity to induce ROS generation. Studies have demonstrated that in human β-cells exposed to various types of saturated or unsaturated long-chain and very-long-chain fatty acids, the degree of lipotoxicity correlates closely with both the saturation level and the chain length of the fatty acids, with very-long-chain FFAs resulting in increased peroxidation.[53] Furthermore, hydrogen peroxide (H2O2) is more effective than long-chain FFAs in promoting peroxidation within β-cell peroxisomes and mitochondria.[54] Furthermore, mitochondrial dysfunction induced by lipotoxicity is a critical contributor to β-cell impairment. The excessive influx of FFAs into mitochondria disrupts normal energy metabolism, thereby reducing membrane potential,

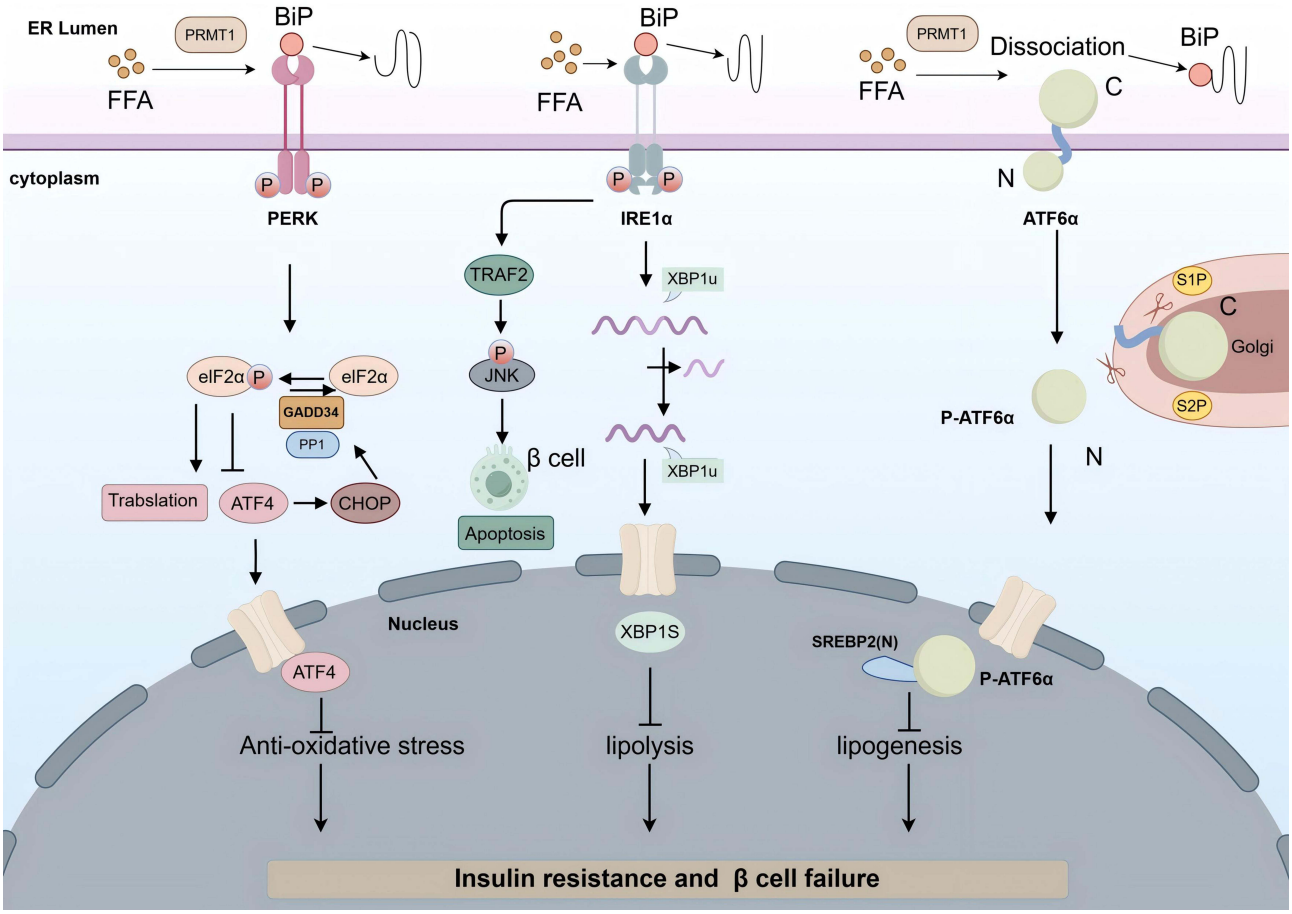


Figure 2 FFA affects endoplasmic reticulum stress (By Figdraw: ISAWRaa0a5). FFA accumulation influences the expression of protein arginine methyltransferase (PRMT1), which promotes the phosphorylation of PERK and the subsequent dissociation of ATF6. Following its dissociation from the heavy chain binding protein BiP, PERK undergoes dimerization and activation, leading to the phosphorylation of eukaryotic translation initiation factor α (eIF2α). This phosphorylation of eIF2α selectively activates the translation of downstream transcription factor 4 (ATF4) and its target gene, CHOP. CHOP, in turn, upregulates the expression of GADD34, which binds to protein phosphatase 1 (PP1c) and facilitates the dephosphorylation of eIF2α, thereby establishing a negative feedback loop. ATF4 also induces the expression of genes involved in the anti-oxidative stress response, contributing to insulin resistance and pancreatic β-cell failure. Furthermore, FFA accumulation promotes the dissociation of IRE1α from BiP and its phosphorylation. IRE1α is capable of cleaving the mRNA of the transcription factor X-box DNA binding protein 1 (XBP1), thus regulating lipolysis and exacerbating lipotoxicity. Additionally, IRE1α interacts with tumor necrosis factor receptor-associated factor 2 (TRAF2) and activates apoptosis signal-regulated kinase 1 (ASK1), which triggers the JNK-mediated pro-apoptotic pathway, leading to pancreatic β-cell apoptosis. In the resting state, the C-terminus of ATF6 is situated in the ER lumen, while its N-terminus extends into the cytoplasm. When unfolded or misfolded proteins accumulate in the ER membrane, the C-terminal CD1 domain senses this stress, resulting in the release of transcription factor 6α (ATF6α) from BiP and its transport to the Golgi compartment, where it undergoes regulated cleavage by the proteases S1P and S2P. The cleaved ATF6α then forms a complex with SRE-bound SREBP2 N to inhibit lipogenesis, thereby mitigating lipotoxic damage.

limiting ATP production, and enhancing ROS generation. These alterations, in turn, amplify OS, establishing a detrimental feedback loop that ultimately precipitates β-cell damage and death.

Signaling pathways activated by ROS include nuclear factor kappa B (NF-kB), p38 mitogen-activated protein kinase (MAPK), NH2-terminal Jun kinases/stress-activated protein kinases (JNK/SAPK), and protein kinase C (PKC). While ROS are recognized for inducing cellular dysfunction through various mechanisms, including cell proliferation, hypertrophy, and apoptosis,[51,55] the specific process by which ROS induce β-cell apoptosis under lipotoxic conditions has yet to be fully elucidated. The limited expression of antioxidant enzymes in pancreatic β-cells renders them particularly vulnerable to OS.[56] Research indicates that the accumulation of ROS impairs insulin signaling at multiple levels. Ogihara demonstrated in studies involving Sprague-Dawley rats and 3T3-L1 cells that ROS activation triggers the NF-kB pathway and disrupts the normal subcellular distribution of phosphatidylinositol 3-kinase, thereby inducing insulin resistance.[57] In the same year, Michael also showed through in vitro experiments that ROS activates protein kinase C-1 (PKC-1), which regulates the tyrosine phosphorylation of insulin receptor substrate-1, consequently leading to insulin resistance.[58] Our findings indicate that ROS accumulation activates a cascade of signaling pathways that result in

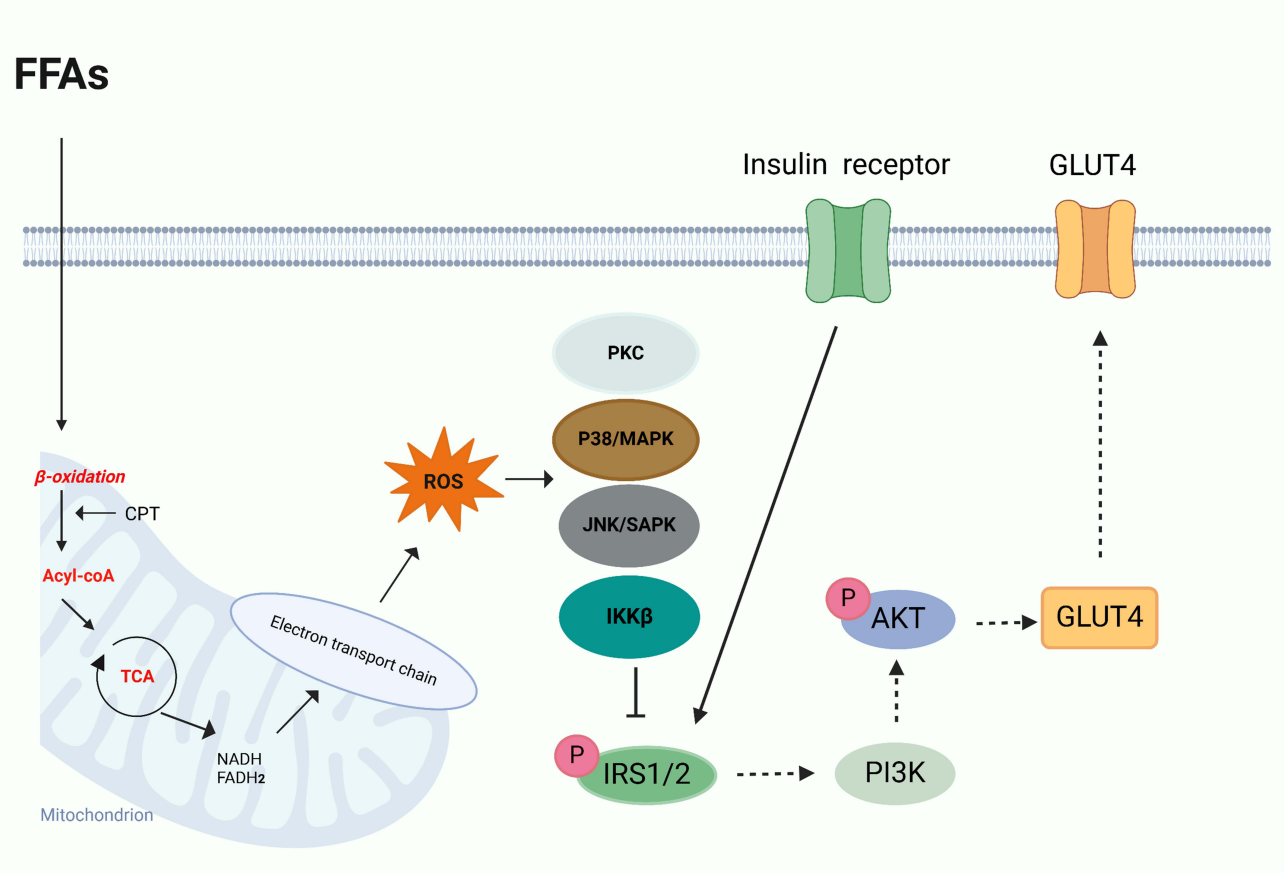


Figure 3 Lipotoxicity activates OS and mitochondrial dysfunction in pancreatic β-cells. The accumulation of FFAs leads to increased beta oxidation, resulting in the production of excess acetyl-CoA, which subsequently enters the tricarboxylic acid (TCA) cycle. This cycle becomes overloaded, generating elevated levels of NADH and $FADH_2$, which enhance the activity of the electron transport chain. This heightened activity results in the overproduction of ROS, contributing to oxidative stress and mitochondrial dysfunction. The excessive generation of ROS adversely affects insulin signaling by activating stress kinases, including c-Jun N-terminal kinase (JNK), IκB kinase beta (IKKβ), p38 MAPK, and protein kinase C (PKC). Consequently, the phosphorylation of insulin receptor substrate (IRS) at serine residues inhibits insulin signaling and induces insulin resistance. Created in BioRender. Wu, Y (2024) https://BioRender.com/l04l119.

the degradation of insulin receptor substrate 1 and 2 proteins, impairs insulin signaling pathways in the liver and skeletal muscle, contributes to insulin resistance, and promotes the progression of T2DM (Figure 3).

OS functions both as a cause and consequence of mitochondrial dysfunction induced by lipotoxicity.[59] Mitochondrial dysfunction, resulting from lipotoxicity, subsequently contributes to the development of IR.[60] FFAs disrupt the proton gradient across the mitochondrial intermembrane space, augment proton conductance, and inhibit ATP synthase-mediated oxidative phosphorylation of ADP, ultimately triggering the release of Ca2+, inducing an energy crisis, and promoting cell death.[61] Furthermore, FFAs excessively activate inducible nitric oxide synthase, resulting in elevated nitric oxide, which damages mitochondrial DNA and induces β-cell apoptosis.[62] A substantial body of evidence supports that excessive FFA accumulation, whether through direct or indirect mechanisms, causes mitochondrial dysfunction. In both isolated human and rat islets, elevated FFA concentrations impair β-cell functionality by inducing OS; in cultured β-cell lines, FFAs elevate ROS levels, decrease insulin secretion and content, and increase apoptosis rates.[63,64] Perfusion studies have shown that the infusion of oleic acid or lipids into healthy rat results in elevated OS markers and reduced insulin gene expression.[65] Another potential mechanism by which FFAs and ROS compromise mitochondrial function may involve the activation of uncoupling protein 2, which may interfere with mitochondrial function by initiating uncoupling.[66] Although UCP2-mediated uncoupling offers protection against excessive ROS and OS, it also diminishes ATP availability, which is crucial for insulin synthesis and secretion. Thus, the upregulation of UCP2 expression could contribute to the adverse effects of FFAs and ROS on β-cell function. Finally, NADPH oxidase (NOX) proteins may mediate lipotoxicity-induced OS in the context of T2DM. Saturated FAs elevate NOX protein levels and activation, which leads to β-cell dysfunction and

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apoptosis.[67–69] Furthermore, abnormal activation of NOX enzymes may also affect other organs, encompassing the liver and adipose tissue, serving a pivotal function in the progression of diabetes.[70,71]

Lipotoxicity Triggers Apoptosis in Pancreatic β-Cells

The dysfunction or failure of pancreatic β-cell activity represents a pivotal pathological connection in T2DM. These β-cells are essential for glucose regulation via insulin secretion and the maintenance of glucose-lipid metabolic balance. Under typical circumstances, the binding of insulin to its receptor initiates the activation of tyrosine kinase, which subsequently phosphorylates IRS-1/2. This phosphorylation enhances the expression of glucose transporters via the phosphatidylinositol 3-kinase and Akt pathway, facilitating glucose uptake by cells. However, pancreatic β-cells are particularly vulnerable to elevated lipid levels and the resulting lipotoxic effects. Lipotoxicity impedes insulin signaling, diminishing insulin sensitivity in target cells, thereby reducing insulin efficacy and disrupting glucose metabolism. These signaling pathways simultaneously impact the β-cells themselves, culminating in their dysfunction and eventual apoptosis. Research has demonstrated that prolonged elevations in FFAs not only impair β-cell function but also promote β-cell apoptosis.[72] FFAs may initiate cell apoptosis through various mechanisms, including membrane disruption, cytoskeletal alterations, cell cycle arrest, ER stress (mediated by CHOP and JNK activation), OS, mitochondrial dysfunction, and ceramide accumulation.

Lipotoxicity initially disrupts the integrity of β-cell membranes, resulting in a reduction of membrane fluidity and an increase in permeability. This membrane damage subsequently triggers apoptotic signaling cascades, promoting cellular apoptosis. Additionally, lipotoxicity is known to induce cytoskeletal remodeling through the activation of RhoA and ROCK signaling pathways, further exacerbating apoptosis. Furthermore, lipotoxicity causes cell cycle arrest by inhibiting proliferation through the activation of p53 and p21 pathways while also facilitating apoptotic processes. In addition, lipotoxicity induces ER stress and OS, which activate the UPR and lead to apoptosis. Xiaoqing demonstrated that lipid-induced ER stress is strongly correlated with β-cell dysfunction, causing a disruption in the balance between protein folding and insulin synthesis.[73] Notably, in 1995, Kolesnick introduced the concept of ceramide-mediated apoptosis,[74] in which saturated FFAs, such as palmitate, serve as precursors for de novo ceramide biosynthesis, culminating in ceramide accumulation. In 1998, Shimabukuro first reported ceramide-induced lipotoxicity in pancreatic β-cells, showing that increased ceramide synthesis was a key mediator of β-cell apoptosis in obese and T2DM rat models.[75] The elevated ceramide content and subsequent β-cell apoptosis were found to correlate with increased expression of serine palmitoyltransferase (SPT), a critical enzyme involved in ceramide synthesis, while inhibition of SPT was shown to prevent apoptosis. Similarly, prolonged exposure of human islets to FFA mixtures resulted in enhanced β-cell apoptosis, which could be partially alleviated by ceramide synthesis inhibitors.[76]

In conclusion, lipotoxicity disrupts insulin signaling via several mechanisms, including damage to the cell membrane, cytoskeletal alterations, cell cycle arrest, ER stress, OS, and ceramide accumulation. These processes impair insulin responsiveness in target cells, induce apoptosis in pancreatic β-cells, and diminish insulin secretion, thereby accelerating the development and progression of T2DM.

Lipotoxicity-Induced Inflammation in Pancreatic β-Cells

Saturated FAs are capable of directly triggering OS and ER stress, thereby initiating inflammatory pathways within pancreatic β-cells.[77] Palmitate has been shown to stimulate the production of pro-inflammatory cytokines, encompassing IL-1β, which in turn activates IL-1β receptor signaling and leads to the subsequent synthesis of IL-6, IL-8, and various chemokines (CCL2, CXCL1) in pancreatic β-cells.[78] However, the extent to which the pro-inflammatory response contributes directly to β-cell glucolipotoxicity remains a subject of ongoing debate. Some studies suggest that palmitate induces pancreatic β-cells to secrete chemokines via Toll-like receptor 4, which attracts M1 pro-inflammatory monocytes/macrophages that subsequently influence the islets. Notably, the depletion of M1 macrophages/monocytes prior to palmitate ester infusion has been shown to protect mice from β-cell dysfunction and to preserve β-cell gene expression.[79] These findings indicate that the interaction between palmitate and immune cells serves a critical function in inflammation-driven pancreatic β-cell dysfunction.

Several studies have suggested that the accumulation of FAs triggers inflammatory responses in pancreatic β-cells, thus accelerating the onset and progression of T2DM. Esteve demonstrated that palmitic acid-induced pro-inflammatory responses in human islets closely resembled CCL2 expression observed in β-cells from T2DM patients, potentially leading to inflammatory cell infiltration within the islets and further aggravating β-cell dysfunction.[16] Lytrivi highlighted that inflammation induced by lipotoxicity was strongly linked to OS and ER stress, together driving β-cell apoptosis and functional decline.[13] Furthermore, Sui reported that FA accumulation activated inflammatory pathways, including NF-kB and the NOD-like receptor protein 3 inflammasome, triggering the release of pro-inflammatory cytokines that not only directly impair pancreatic β-cells but also enhance IR by disrupting insulin signaling pathways.[80] These findings underscore the potential of modulating inflammatory responses as a strategy to protect β-cell function and delay the progression of T2DM.

In conclusion, the onset and progression of T2DM are accelerated by lipotoxicity through the induction of inflammatory responses in pancreatic β-cells, ultimately resulting in β-cell dysfunction and apoptosis.

Research Progress in Anti-Lipotoxicity Treatment

Caloric Restriction and Exercise

Given the rising prevalence of modern high-calorie diets and sedentary lifestyles, caloric restriction and physical activity have assumed greater significance in the management of disease. Caloric restriction and exercise have been demonstrated to mitigate T2DM through the reduction of pancreatic fat accumulation and the alleviation of lipid toxicity. According to Lytrivi, the Diabetes Remission Clinical Trial revealed that nearly 50% of T2DM cases were reversed in patients adhering to a very low-calorie diet for 3–5 months.[13] Furthermore, fat accumulation within the human pancreas predominantly occurs in adipocytes, which may occupy up to 20% of pancreatic tissue. Localized lipolysis is proposed to induce β-cell lipotoxicity via paracrine mechanisms. In rodent models, caloric restriction has been shown to prevent IR and islet dysfunction in streptozotocin-induced T2DM rats.[81] These studies have demonstrated that caloric restriction can significantly reduce fat accumulation and improve blood glucose levels. Additionally, a systematic review and network meta-analysis by Pan explored the effects of various exercise modalities on T2DM patients. It was found that both aerobic and resistance exercises had comparable effects in improving metabolic parameters and enhancing physical fitness.[82] These findings suggest that exercise interventions are effective in reducing pancreatic fat accumulation and correcting glucose metabolism disturbances. Collectively, these results underscore the importance of caloric restriction and physical exercise in alleviating pancreatic fat and improving the pathophysiology of T2DM. By controlling caloric intake and increasing physical activity, IR can be markedly reduced, islet function protected, and glycemic control improved in diabetic patients.

Metformin

Metformin (1,1-dimethylbiguanide), derived from Galega officinalis (French lilac),[83] serves as an insulin sensitizer and exerts beneficial effects on pancreatic β-cells, particularly under conditions of lipotoxicity. It has been shown to inhibit hepatic gluconeogenesis, reduce hepatic glucose production, and lower fasting blood glucose levels, likely through the activation of AMP-activated protein kinase (AMPK). AMPK functions to suppress lipid synthesis by phosphorylating and inactivating key enzymes involved in lipogenesis.[84] In rat hepatocytes, activation of AMPK by metformin has been observed to downregulate the mRNA expression of SREBP-1c and its associated lipogenic target genes, thus modulating energy metabolism, inhibiting hepatic lipid synthesis, and promoting FA oxidation. This, in turn, reduces the interference with insulin signaling pathways caused by lipotoxicity.[85] Similarly, Lin demonstrated that metformin lowers hepatic nSREBP-1 levels and markedly reduces hepatic lipid accumulation in insulin-resistant ob/ob mice.[86]

Various mechanisms underlying the anti-lipotoxic effects of metformin have been explored by researchers. Foretz proposed that metformin might modulate gut microbiota and influence bile acid metabolism, which in turn could enhance insulin sensitivity and regulate lipid metabolism.[87] Pernicova further emphasized that metformin's anti-lipotoxic effects are, in part, attributable to its influence on adipocyte function. Specifically, metformin has been shown to mitigate adipocyte hypertrophy and reduce the secretion of inflammatory factors, leading to a reduction in systemic inflammation

and improved IR.[88] Additionally, studies by Wang have revealed that when metformin is combined with other therapeutic agents, synergistic effects on blood glucose reduction and lipid metabolism enhancement are observed, thereby highlighting the significant clinical potential of metformin in the treatment of lipotoxicity.[89]

Glucagon-Like Peptide-1 (GLP-1) Analogs

GLP-1 analogs serve as therapeutic agents for T2DM by binding to G protein-coupled receptors, thereby activating adenylate cyclase and elevating cyclic adenosine monophosphate levels. This, in turn, triggers protein kinase A activation, which promotes insulin secretion. Despite these well-documented effects, the precise mechanisms through which GLP-1 analogs mitigate lipotoxicity remain incompletely understood. It has been reported that GLP-1 influences lipid metabolism in human adipocytes, reduces fat accumulation, and alleviates lipotoxicity. Additionally, GLP-1 has been shown to induce natriuresis in healthy individuals and insulin-resistant obese men, suggesting its involvement in regulating fluid and electrolyte balance, which indirectly impacts lipid metabolism. The therapeutic efficacy of GLP-1 analogs could be enhanced by conjugating them with molecules such as FAs or albumin to form long-acting peptide derivatives, thereby prolonging their half-life in vivo.[90] This modification not only stabilizes the analogs but may also enhance their capacity to regulate lipid metabolism. A systematic review and network meta-analysis conducted by Yao provided evidence that GLP-1 receptor agonists markedly improve glycemic control, reduce body weight, and lower blood lipid levels in T2DM patients, supporting the hypothesis that GLP-1 analogs can modulate metabolic status through multiple pathways, ultimately reducing lipotoxicity.[91] In addition, research by Tanday underscored the significance of GLP-1 receptor ligands in metabolic responses and their associated benefits, further corroborating the potential of GLP-1 analogs in anti-lipotoxicity therapies.[92]

Thiazolidinediones (TZDs)

TZDs are oral medications commonly utilized in the treatment of T2DM, primarily by enhancing insulin sensitivity and lowering blood glucose levels.[93] The fundamental structure of TZDs consists of a thiazolidinedione ring, which interacts with peroxisome proliferator-activated receptor γ (PPARγ) to regulate both glucose and lipid metabolism.[94] Despite a decline in the use of TZDs in recent years—attributable to concerns regarding the association of rosiglitazone with increased cardiovascular risk and pioglitazone's potential link to bladder cancer—evidence continues to support their protective effects against glucolipotoxicity. Research conducted by Yasmin and Nanjan examined the synergistic effects of TZDs and PPAR receptors in anti-diabetic therapy. Their findings indicated that PPARγ activation not only regulates glucose metabolism but also influences lipid metabolism, mitigates abnormal lipid accumulation in non-adipose tissues, and reduces lipotoxicity-induced damage to pancreatic β-cells and insulin-responsive tissues. Furthermore, rosiglitazone has been shown to prevent FFA-induced downregulation of PPARγ and to preserve insulin secretion function in human pancreatic β-cells.[95] In a comprehensive review of TZDs as anti-diabetic agents, Nanjan emphasized the importance of these drugs in regulating lipid metabolism. The study proposed that through PPARγ activation, TZDs enhance fatty acid uptake in adipose tissue, diminish lipogenesis, and consequently reduce plasma FFA concentrations, thereby mitigating lipotoxicity-induced interference with insulin signaling. This mechanism facilitates improved IR and enhances insulin-mediated glucose uptake. As such, TZDs exhibit a dual mechanism of action that underpins their effectiveness in treating T2DM by counteracting lipotoxicity. In conclusion, TZDs are pivotal in improving IR in T2DM patients through the activation of PPARγ, the regulation of glucose and lipid metabolism, and the reduction of lipotoxicity.

Molecular Chaperones

In recent decades, molecular chaperones have emerged as promising agents in the treatment of lipotoxicity. These small molecular compounds function to stabilize protein conformation and enhance the protein-folding capacity within the ER. Among the most extensively studied chaperones are 4-phenylbutyric acid (PBA) and tauroursodeoxycholic acid (TUDCA), both of which are characterized by their favorable safety profiles. In studies in leptin-deficient (ob/ob) mice, PBA and TUDCA were shown to alleviate ER stress and enhance glucose-stimulated insulin secretion.[96] Additionally, research involving obese or overweight, non-diabetic individuals indicated that pre-treatment with PBA could partially prevent β-cell dysfunction prior to lipid infusion, suggesting a potential protective role against β-cell lipotoxicity. However, further research is needed to elucidate whether this protective effect is mediated via a reduction in ER stress.

Table 1 Anti-Lipotoxic Treatment

Caloric restriction and exercise	• Calorie restriction can reduce pancreatic fat accumulation and improve blood sugar levels. • Exercise intervention can reduce pancreatic fat accumulation and correct glucose metabolism disorders.	[81,82]
Metformin	• Activating AMPK reduces lipogenesis gene expression and promotes fatty acid oxidation. • Modulate intestinal microbiota and improve lipid metabolism. • Reduce fat cell hypertrophy and secretion of inflammatory factors, reduce systemic inflammation levels and improve insulin resistance.	[84–88]
Glucagon-like peptide-1 (GLP-1) analogs	• Combine with fatty acids or albumin and other substances to extend half-life and enhance lipid decomposition. • Induces natriuresis, regulates body fluid and electrolyte balance, indirectly affects lipid metabolism pathways and improves blood sugar.	[90,91]
Thiazolidinediones (TZDs)	• Binds to peroxisome proliferator-activated receptor gamma (PPARγ) to regulate glucose and lipid metabolism, promote fatty acid uptake in adipose tissue and reduce lipogenesis.	[94,95]
Molecular chaperones	• PBA and TUDCA were shown to alleviate ER stress and enhance glucose-stimulated insulin secretion. • GRP78/BiP inhibits the misfolding of the endoplasmic reticulum and the formation of β-sheet aggregates, reducing the toxic effects on pancreatic β-cells. • polydatin protects against lipotoxicity-induced pancreatic β-cell dysfunction by inhibiting ER stress and excessive autophagy.	[29,96,97]

Molecular chaperones are integral to protein folding and cellular homeostasis, with their dysfunction being closely linked to the pathogenesis of T2DM. It has been demonstrated that chaperones, such as GRP78/BiP, HSP70, and HSP40/DnaJ, are capable of preventing the misfolding of human amylin and the formation of β-sheet aggregates, thereby mitigating toxic effects on pancreatic β-cells and influencing the progression of T2DM.[97] According to Nourbakhsh, ER stress serves a pivotal function in β-cell lipotoxicity, and markedly elevated serum GRP78 levels in T2DM patients may serve as an indicator of the interaction between ER stress and glucose metabolism, with the GRP78/BiP chaperone protein restoring ER homeostasis by modulating the UPR. Additionally, Jin found that polydatin protects against lipotoxicity-induced pancreatic β-cell dysfunction by inhibiting ER stress and excessive autophagy,[29] further supporting the involvement of molecular chaperones in mitigating lipotoxicity (Table 1).

Others

Beyond the previously discussed therapeutic approaches, additional research avenues warrant further exploration. Kuzmenko proposed that ceramides are pivotal in regulating apoptosis and the onset of IR.[61] In 2008, Guichard suggested that the NOX family of NADPH oxidases may be instrumental in the pathogenesis of metabolic syndrome and diabetes, affecting both the liver and islet cells.[98] Subsequently, in 2010, Yuan demonstrated that ROS generated by NADPH oxidase 2 mediated FFA-induced dysfunction and apoptosis of pancreatic β-cells through activation of the JNK, p38 MAPK, and p53 signaling pathways.[68] In 2015, Anvari introduced GLX351322, a novel NADPH oxidase 4 inhibitor, which was shown to enhance glucose tolerance in high-fat diet-induced mice,[71] providing further evidence for the therapeutic promise of targeting the NOX family in the treatment of lipotoxicity. Additionally, other studies revealed that irisin extract mitigated FFA-induced IR and inflammatory responses in pancreatic β-cells by activating the PI3K/AKT/FOXO1 signaling pathway.[27] Plötz explored the structure-toxicity relationship of both saturated and unsaturated FFAs, offering insights into the underlying mechanisms of lipotoxicity in human pancreatic β-cells.[53]

Conclusions

In recent decades, despite considerable scholarly efforts dedicated to investigating lipid toxicity, research has predominantly focused on disparate conditions such as non-alcoholic fatty liver disease, cardiomyopathy, and kidney disease,

with relatively limited attention given to T2DM. Consequently, the development of specific and robust theories for guiding future research has been challenging. This review elucidates that the aberrant accumulation of lipids in non-adipose tissues contributes to the progression of T2DM via multiple mechanisms, including ER stress, OS, mitochondrial dysfunction, β-cell apoptosis, and β-cell inflammation. These findings underscore the significant role of lipid toxicity in the pathogenesis and progression of T2DM. In clinical practice, the management of T2DM typically emphasizes enhancing insulin sensitivity and stimulating insulin secretion. Key therapeutic strategies encompass caloric restriction, physical activity, metformin, GLP-1 receptor agonists, thiazolidinediones, molecular chaperones, and other approaches. By elucidating the precise mechanisms of action of these therapeutic strategies in lipid toxicity, we can offer novel insights and approaches for the treatment of T2DM and associated metabolic disorders. Future research endeavors should prioritize elucidating the mechanisms of lipid toxicity at both cellular and molecular levels, while also investigating its translational potential for clinical applications.

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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 no conflicts of interest.

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