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A comprehensive review on the mechanistics of free fatty acid-induced insulin resistance and it's therapeutics: Molecular perspectives

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ABSTRACT

Type 2 diabetes mellitus (T2DM) is a multidimensional metabolic disorder characterized by hyperglycemia, insulin insensitivity, and dysfunction and degeneration of β-cells. Increase in the levels of free fatty acids (FFAs) in blood plasma is a typical symptom of obesity and metabolic syndrome, which influences the mechanisms of insulin resistance and β-cell impairment. Acute increase in FFA levels blocks glucose uptake by insulin-sensitive skeletal muscles while chronic increase in FFA levels results in hepatic insulin resistance which causes gluconeogenic flux and lipotoxicity in pancreatic βcells. FFA-induced insulin resistance involves various molecular pathways and generation of lipid intermediates (diacylglycerol and ceramides), activation of serine/threonine kinases (PKC), induction of oxidative and endoplasmic reticulum stresses, and inflammatory signaling via nuclear factor-κB (NF-κB) and toll-like receptor (TLR) signaling pathways. Recent studies have indicated that the fetuin-A-FFA complex is an important endogenous ligand of TLR4 that causes inflammation and metabolic dysregulation. In addition, certain FFAs, especially ω-6 polyunsaturated fatty acids, can elicit ferroptosis which is a new form of lipid peroxidation-mediated cell death in β-cells, thereby expanding the extent of FFA-mediated lipotoxicity. This review covers recent information on the mechanisms and clinical factors related to the role of FFAs in insulin resistance and T2DM pathogenesis, and the contribution of experimental research towards developing therapeutic strategies in normalizing the levels of FFA and inhibiting downstream lipotoxicity-related pathways.

1. Introduction

Free fatty acids (FFAs) are important nutritional factors that serve as signaling molecules in diverse physiological pathways. High concentrations of FFAs have been correlated with increase in insulin resistance, which is a multifaceted mechanism implicated in the pathogenesis of type 2 diabetes mellitus (T2DM) [54,59]. This review discusses the complex role of FFAs in insulin resistance by deregulating metabolism in skeletal muscles, and liver and adipose tissues [48]. This deregulation leads to a series of metabolic disturbances and eventually affects glucose uptake and utilization which is a characteristic of T2DM [51]. This review focuses on the molecular and cellular processes through which FFAs interfere with insulin signaling and impair insulin sensitivity resulting in the development of metabolic syndrome [19]. Excessive levels of FFAs cause lipolysis in important tissues such as liver tissue and skeletal muscles resulting in hepatic steatosis and impaired insulin sensitivity [40]. This is often worsened due to the presence of central obesity resulting in a lipotoxic environment that directly affects the insulin signaling pathways and glucose uptake [21,46]. Increase in the levels of FFAs in circulation also triggers an increase in the levels of serine kinases like p38 and c-Jun N-terminal kinase which in turn prevents the phosphorylation of insulin receptor substrate 1 involved in the insulin signaling pathway [20]. This causes a decrease in the levels of phosphorylation of tyrosine in the insulin receptor and other related

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proteins that suppress downstream signaling and translocation of glucose transporter 4 to the cell membrane [19]. Our research group is also involved in studying the mechanisms and ameliorations of insulin resistance mediated type 2 diabetes pathophysiology [44,58]. FFA involvement in insulin resistance is the main emphasis in this review. However, although chronic exposure to FFAs can also influence the functionality and viability of β-cells in the pancreas, such an effect is mentioned only in regard to its contribution to type 2 diabetes mellitus development.

2. Overview of FFA-induced insulin resistance and lipotoxicity

T2DM is a metabolic disorder that affects over 90% of the global population and is one of the most important metabolic disorders worldwide [28]. The epidemiological trend of T2DM in the Indian subcontinent points toward an expected 80 million cases by 2030 [6]. This is not just a statistical increase but an indication of the speed of urbanization leading to people adopting a more sedentary lifestyle thereby outpacing biological evolution. The pathogenesis of T2DM is characterized by a systemic failure of glucose homeostasis that is manifested by a combination of peripheral insulin resistance, defective insulin secretion, and subsequent hyperglycemia. Although the presence of early-stage metabolic stress is obscured by contradictory hyperinsulinemia in pancreatic β-cells, such an overdrive is unsustainable by its very nature as the β-cells begin to experience progressive exhaustion which is made more disastrous due to glucolipotoxicity. The progression of subclinical insulin resistance to clinical diabetes is imminent which leads to the emergence of microvascular and macrovascular complications such as nephropathy and rapid cardiovascular deterioration [25,27].

Insulin resistance in T2DM is not the failure of any one pathway but a multiorgan metabolic disturbance complicated by obesity. Some of the most important consequences of insulin resistance are an increase in the levels of FFAs in the plasma and adiposity-induced metabolic derangement characteristic of T2DM. The classical model of lipid-heparin infusion indicates that an acute spike in FFA can attenuate glucose removal from skeletal muscle in a very short time (2–4 h) [13]. Furthermore, persistently high levels of FFAs in individuals with obesity can cause the liver to enter a state of metabolic inflexibility wherein insulin-induced repression of gluconeogenesis is hindered and glucose production by the liver is constitutive [14].

The objective of this review is to provide a basic overview of the lipid dynamics in T2DM and attempt to fill the gaps in our understanding regarding the interplay between cellular stress and systemic inflammatory cascade. The combination of evidence from clinical studies and experiments on murine models allows us to assess the suitability of targeting FFA metabolism and signaling to reverse rather than to control T2DM.

3. Insulin signaling pathway

The effects of insulin activation depend on the reorganization of the heterotetrameric insulin receptor (IR) (Fig. 1). Upon ligand binding, the intracellular β-subunit kinase domain is autophosphorylated converting it into an IR binding docking site [22,67]. Although the subsequent recruitment of phosphoinositide−3-kinase (PI3K) and the formation of phosphatidylinositol (3,4,5)-triphosphate (PIP3) has been characterized as a linear signal pathway, in disease condition, it represents a weak signal gateway. The PI3K-Akt axis represents the central mechanism in glucose regulation. The phosphorylation of tyrosines on IRS is enabled by the interaction with the p85 regulatory subunit of PI3K and results in increased PIP3 levels. This lipid secondary messenger stabilizes Akt

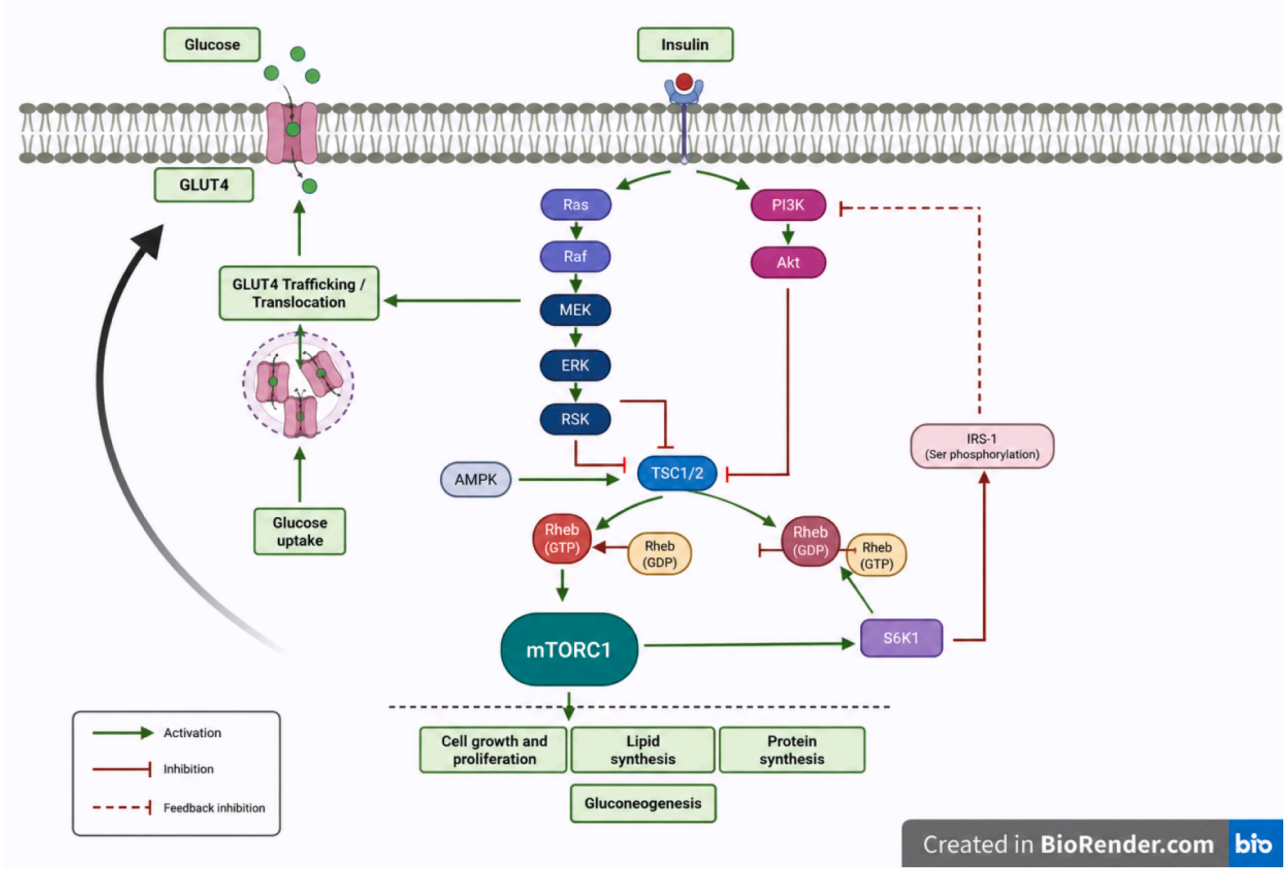


Fig. 1. Insulin signaling pathway and glucose uptake mechanism.

(protein kinase B) on the plasma membrane and activates it following recruitment of pyruvate dehydrogenase kinase 1 (PDK1) [62]. The physiological outcome of this cascade is tissue-specific. Activated Akt coordinates the translocation of glucose transporter type 4 (GLUT4) from the cytosol to the cell surface in vesicles in myocytes and adipocytes to enable glucose entry [64]. This axis, however, is decoupled in the insulin-resistant liver. Akt cannot adequately suppress the forkhead box O1 (FOXO1) transcription factor and the gluconeogenic flux is uncontrolled even in the presence of high systemic levels of insulin [24]. Although the mitogen-activated protein kinase (MAPK) pathway controls mitogenic growth, it is still mostly independent of metabolic homeostasis [55].

The difference lies in the "serine/tyrosine" switch. The classic lipotoxic stress-induced scaffolding of IRS−1 is inhibited when there is lipotoxic stress. Inhibitory serine phosphorylation is catalyzed by proinflammatory kinases such as c-Jun N-terminal kinase (JNK), Iκb kinase (IKK), and extracellular signal-regulated kinase (ERK). These not only reduce the rate of the signal but prevent the binding of the p85 regulatory subunit of PI3K thereby quenching the downstream Akt signal before it can reach the plasma membrane [34]. The main mediator between increased levels of FFAs and peripheral glucose intolerance is this molecular uncoupling.

4. Role of free fatty acids in insulin resistance

The pathological feed-forward loop consequent to increase in FFA levels has been described in the literature. Obesity is metabolically marked by the sustained increase of FFAs in circulation, which is both an indicator and a cause of whole-body insulin resistance [12,13,53]. Although FFAs play an important role in the body as an energy source made via de novo lipogenesis and derived from the diet, their chronic induction in the post-prandial condition is an indication of failure of the role of adipose tissues.

In homeostatic condition, insulin is a strong anti-lipolytic hormone which suppresses the hormone-sensitive lipase. In the insulin-resistant condition, this suppression does not take place in the adipose tissue (Frayn et al., 2001). This causes a free efflux of lipids in the portal circulation, which not only enhances caloric accessibility but initiates a vicious circle of damage and impaired insulin signaling that facilitates lipolysis and increases the levels of FFAs further promoting peripheral insulin resistance. This loop is effective in converting the adipose tissues into energy storage tissues for conditions of lipotoxic stress that may exceed the metabolic ability of the liver and skeletal muscle. Although the relationship between lipolysis and insulin resistance has been well-studied, the point at which the process of inflammation in adipose tissue becomes irreversible remains unclear.

4.1. Temporal dynamics: Acute lipotoxicity and peripheral resistance

Experimental lipid-heparin infusion models have been used to determine the causal relationship between increased lipid levels and metabolic dysfunction. An acute increase in systemic FFA levels can rapidly reduce insulin sensitivity throughout the body within just two to four hours [13]. A euglycemic-hyperinsulinemic clamp has been used to determine that over 80% of glucose is dissipated by skeletal muscles indicating that it is the primary anatomic location of such acute defects. Once plasma free fatty acid (FFA) levels normalize, insulin sensitivity is restored almost immediately, indicating that the initial impairment was a transient metabolic effect rather than permanent structural damage [13].

Mechanistically, the rapid development of insulin resistance is facilitated by the intracellular partitioning of lipids. When there is an excess of FFA levels beyond which the mitochondria can oxidize, there is an increase in the levels of long-chain fatty acyl-CoAs. These molecules act as precursors for the rapid synthesis of DAG and ceramides - lipid intermediates which are generated when normal signaling pathways are disrupted. In contrast to neutral triglycerides that are stored as droplets, these bioactive lipids interfere with the recruitment of the IRS−1/PI3K complex thereby effectively preventing muscle response to insulin surge resulting in chronic inflammation.

4.2. Organ-specific consequences of chronic FFA exposure

Acute increases in FFA levels present a short-term metabolic risk. However, when FFA levels are raised chronically owing to a sedentary lifestyle and prolonged consumption of high-fat diets, the metabolic identities of skeletal muscle, liver, and pancreas are altered. Fig. 2 presents both the acute and chronic effects of FFAs.

Increased levels of lipids have consequences beyond the disruption of signaling pathways in muscles. The accumulation of intramyocellular lipids (IMCLs) leads to chronic inflammation resulting in a constitutive state of activation of DAG-PKC. This leads to prevention of IRS−1 serine phosphorylation which inhibits translocation of GLUT4 to the sarcolemma [36]. The ultimate outcome is not a delay in glucose uptake but chronic intracellular signaling impairment to insulin and consequent metabolic dysregulation leads to a state of fixed insulin resistance.

The response of the liver to chronic lipid flux is determined by the proximity of the visceral adipose tissue to the portal vein. According to the "portal FFA hypothesis", the liver is exposed to a large amount of lipids in the visceral deposits [8]. This results in an increase in the levels of hepatic acetyl-CoA which is both a substrate and an allosteric activator of the gluconeogenic apparatus thereby depriving the liver of its metabolic brake. Insulin is unable to inhibit glycogenolysis or gluconeogenesis resulting in unregulated fasting hyperglycemia typical of advanced T2DM [14,56]. During this time, excessive production of very low-density lipoprotein (VLDL) is seen which worsens the atherogenic dyslipidemia that characterizes most cases of metabolic syndrome.

The effects of chronic lipid exposure are probably the most destructive in the pancreatic islets. While acute FFA exposure may have contradictory effects such as facilitating insulin discharge through G-protein-coupled receptor 40 (GPR40) signaling, chronic lipotoxicity is destructive via the dual mechanism of ER stress and oxidative stress. Recent evidence has revealed the type of cell death that is caused by certain lipid species. While saturated FFAs carry out conventional apoptosis, ω−6 PUFAs, in particular, have been reported to induce ferroptosis (Krummel et al., 2022). This iron-dependent form of lipid peroxidation represents another facet of β-cell exhaustion that culminates in pancreatic failure during T2DM. Ultimately, this process drives structural failure stemming from iron-catalyzed membrane damage.

This multi-modal attack on cells involves several different mechanisms. Increased FFA levels result in the accumulation of long-chain fatty acyl-CoAs, DAG, and ceramides, which are endogenous ligands of the innate immune system and which serve as signal decoys. FFAs trigger a proinflammatory signaling cascade via the activation of the TLR4-fetuin-A complex indicating a link between lipid metabolism and systemic chronic inflammation.

4.3. Summary

The ultimate outcome is an almost complete shift of T2DM to a lipid signaling failure, where the primary issue is no longer caloric excess, but a breakdown in the endocrine and paracrine crosstalk between tissues. In this state, the uncontrolled release of fatty acids from adipose tissue acts as a chronic, maladaptive signal that disrupts cellular metabolism in insulin-sensitive organs. This systemic signaling dysfunction triggers lipotoxicity, which eventually overrides insulin signaling pathways. Developing therapeutic interventions targeting this molecular crosstalk between adipose tissue lipolysis and organ-specific lipotoxicity can help prevent the condition and reverse insulin resistance.

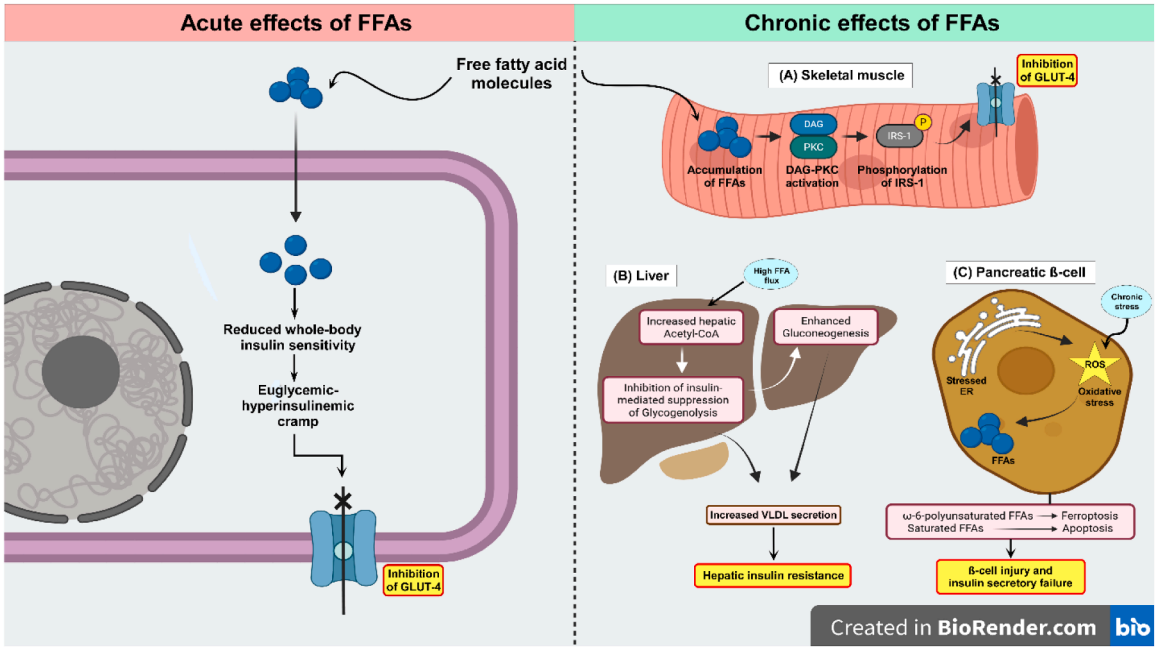


Fig. 2. Acute and chronic effects of FFAs.

5. Molecular mechanisms of FFA-induced insulin resistance

High circulating levels of FFAs affect intracellular lipid metabolism and promote stress and inflammatory mechanisms that eventually result in insulin desensitization. Although the sequence of tissues that are affected may differ, a number of observations have been reported from human and animal studies as well as experiments using cellular models. These observations include the accumulation of toxic fatty acid intermediates, activation of serine/threonine kinases, ER stress, oxidative stress, and activation of the TLR4-fetuin-A pathway. A combination of these mechanisms inhibits IRS-PI3K-Akt signaling and attenuates insulin-stimulated glucose clearance (Fig. 3).

Table 1 provides a list of studies that have attempted to uncover the mechanisms of FFA-induced insulin resistance.

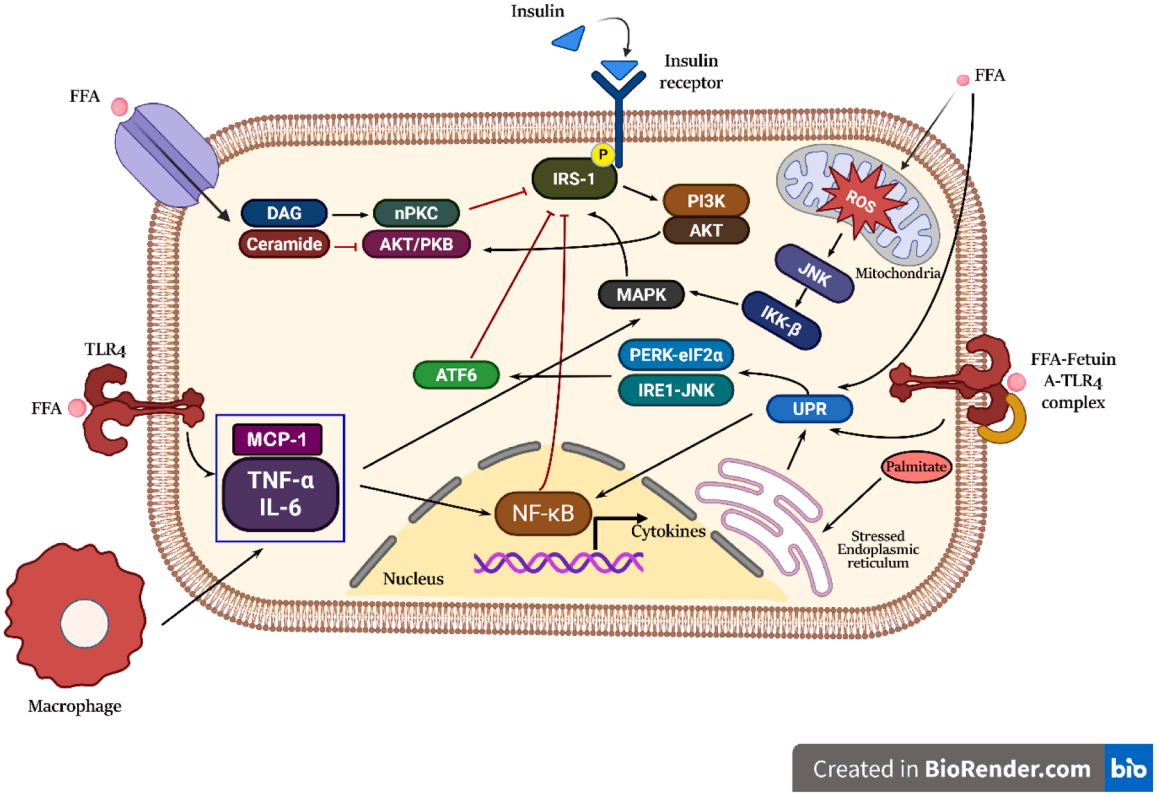


Fig. 3. Mechanisms of insulin resistance.

Table 1
Selected in vivo and ex vivo studies from 2015 to 2025 investigating free fatty acid (FFA)-induced insulin resistance. The table provides a summary of experimental and translational studies investigating the effects of high levels of FFAs and high-fat diet or lipid treatments on insulin sensitivity. [FFA – free fatty acid; HFD – high-fat diet; DAG – diacylglycerol; MCP−1 – monocyte chemoattractant protein−1; SFA – saturated fatty acid; GLUT4 – glucose transporter type 4; IRS – insulin receptor substrate; PKC – protein kinase C; NEFA – non-esterified fatty acid; ER – endoplasmic reticulum; Sptlc2 - serine palmitoyltransferase long chain base subunit 2].

No	Model	Intervention	Key findings	Reference
1.	Healthy humans (lipid/heparin infusion, euglycemic-hyperinsulinemic clamp)	Lipid + heparin infusion to increase plasma FFA levels	Acute FFA elevation rapidly decreased whole-body insulin-stimulated glucose uptake (muscle); reversible after normalization	[42]
2.	HFD-fed C57BL/6 mice (chronic HFD)	HFD (various durations)	HFD causes accumulation of DAG/ceramide in liver and muscle leading to insulin resistance; composition and duration affect lipid species	[47]
3.	db/db mice and HFD mice (ceramide studies)	HFD; genetic obesity models	High ceramide content is linked to hepatic and muscle insulin resistance; inhibiting ceramide synthesis improves insulin signaling	[52]
4.	Liver-specific Sptlc2 knockdown mice	Genetic silencing of Sptlc2 (reduces ceramide synthesis)	Reduced hepatic ceramide levels improved insulin signaling and glucose metabolism in HFD mice	Imierska et al.
5.	Human overfeeding/ metabolic studies	Overfeeding/ weight gain interventions	Overfeeding increases circulating fetuin-A and markers of insulin resistance; supports fetuin-A's role with FFA	[43]
6	Fetuin-A knockdown mice (HFD)	Genetic/ therapeutic reduction of fetuin-A	Fetuin-A reduction decreased adipose macrophage infiltration and MCP−1 expression and improved insulin sensitivity	[49]
7	Palmitate-treated C2C12 myotubes (in vitro)	Palmitate incubation (SFA)	Palmitate induces insulin resistance by impairing GLUT4 translocation, remodeling actin, and increasing phosphorylation of serine residues on IRS	[70]
8	Human skeletal muscle biopsy - lipid localization study	Observational; lipidomics of muscle compartments	Subcellular localization of DAG and sphingolipids affects insulin signaling; membrane-associated DAG correlates with PKC activation	[50]
9	Human clamp –reviews and meta-analyses	NEFA/lipid infusion protocols (meta-analyses)	Meta-analyses and reviews confirm acute NEFA elevation decreases muscle glucose uptake and impairs hepatic insulin suppression	[41] [31];
10	ER stress–ceramide link, mouse studies	ER stress induction increases Sptlc2 and ceramide	ER stress upregulates Sptlc2, increases ceramide, and impairs hepatic insulin signaling	[45]
11	Human study: increased plasma fatty acid clearance versus concentration	Observational/ interventional metabolic studies	Increased fatty acid clearance, not just concentration, affects ectopic fat deposition and insulin resistance risk	[18]

5.1. Intracellular accumulation of lipid intermediates (DAG and ceramides)

Intracellular accumulation of DAG and ceramides occurs when FFA levels exceed beyond the oxidative potential of the mitochondria and is considered to be one of the most common mechanisms in FFA-induced insulin resistance.

5.1.1. DAG–PKC activation

Overproduction of FFA results in DAG overload in muscles and liver. DAG promotes the generation of novel protein kinase C (nPKC) isoforms, specifically PKCθ in muscles and PKCε in the liver [33,38]. Phosphorylation of serine residues of IRS−1 by PKC impairs its capacity to be phosphorylated by insulin stimulation. This further inhibits the binding of PI3K to IRS which ultimately prevents the activation of Akt and translocation of GLUT4. Studies on human biopsy samples have revealed close associations between intramyocellular levels of DAG, PKC activity, and insulin resistance in the body [36].

5.1.2. Ceramide accumulation

Increased FFA levels also result in the production of ceramides such as palmitate which directly inhibit Akt activation by activating protein phosphatase 2 A (PP2A) or inhibit Akt translocation to the membrane [60]. Ceramides also affect the development of mitochondrial reactive oxygen species (ROS) and increase apoptosis in insulin-sensitive tissues.

5.2. Mitochondrial dysfunction and oxidative stress

When FFAs accumulate intracellularly beyond the oxidative potential of mitochondria, β-oxidation in the mitochondria is affected resulting in the formation of lipid-derived ROS. These ROS can be activated by redox-sensitive serine/threonine kinases.

5.2.1. JNK, IKK, and p38 MAPK

These kinases phosphorylate the serine residues on IRS and block downstream insulin signaling [34]. Mitochondrial overload also compromises ATP generation, alters membrane potential, and increases uncoupling protein activity which also leads to metabolic inflexibility [7].

5.2.2. ER stress

Chronic exposure to increased FFAs results in the buildup of unfolded proteins leading to the unfolded protein response (UPR). Saturated FFAs, specifically palmitate, are embedded in the ER membrane making it more rigid and disturbing ER calcium homeostasis [65]. Prolonged UPR activates protein kinase R-like endoplasmic reticulum kinase-eukaryotic initiation factor 2 alpha (PERK–eIF2α), inositol-requiring enzyme 1-JNK (IRE1–JNK), and activating transcription factor 6 (ATF6). These signaling pathways inhibit insulin receptor expression by phosphorylating serine residues on IRS−1 and inducing the expression of proinflammatory cytokines. ER stress also activates β-cell non-function by inducing apoptosis and blocking insulin biosynthesis.

5.3. Inflammatory signaling and NF-κB activation

FFAs cause low-grade inflammation in tissues. Tumour necrosis factor alpha (TNFα), interleukin−6 (IL-6), and monocyte chemoattractant protein−1 (MCP−1) are released by adipocytes and infiltrating macrophages and these cytokines activate the JNK and IKK pathways. TNFα and IL-6 promote phosphorylation of serine residues on IRS−1, increased expression of suppressor of cytokine signaling (SOCS) protein, and reduced autophosphorylation of the insulin receptor. Chronic inflammation is characteristic of insulin resistance as a consequence of obesity and is closely linked to increased levels of FFAs. JNK impairs insulin signaling by phosphorylating IRS−1 at the inhibitory serine residue Ser312 (corresponding to Ser307 in rodents), thereby reducing its ability to effectively transmit insulin receptor signals [5]. In contrast to initial speculations, TLR4 is not directly bound to and activated by FFAs. Instead, the liver-derived glycoprotein, fetuin-A, binds to FFAs and the resultant complex functions as an endogenous ligand of TLR4 in adipocytes and macrophages [49]. Activation of TLR4 triggers NF-κB activation, upregulation of proinflammatory cytokines, and increased ceramide synthesis via the de novo lipogenesis pathway. These mechanisms combine metabolic and immune responses and can be regarded as important factors of obesity-related chronic inflammation. High serum fetuin-A levels precede insulin resistance and T2DM in humans (Stefan & Haring, 2013).

5.4. Lipid peroxidation and ferroptosis in β-cells

Recent evidence reveals that long-chain PUFAs, specifically ω−6 PUFAs, undergo iron-dependent lipid peroxidation resulting in ferroptosis, a distinct form of cell death regulated by glutathione depletion, glutathione peroxidase 4 (GPX4) inactivation, and accumulation of lipid peroxides. This causes ferroptosis of pancreatic β-cells which possess low inherent antioxidant capacity (Krummel et al., 2022). Ferroptosis results in β-cell failure and can lead to the development of insulin resistance and overt T2DM.

5.5. Summary of mechanistic pathways

FFAs disrupt insulin activity through various interdependent mechanisms. DAG and ceramides suppress the IRS-PI3K-Akt signal and stress induced by ROS and mitochondrial dysfunction inhibit insulin signaling. Increased levels of FFAs result in the activation of innate immunity via TLR4-fetuin-A and dysfunction of β-cells is mediated by ferroptosis and apoptosis. All these processes work in synergy, which is why acute and chronic exposure to FFAs result in insulin resistance and development of T2DM.

6. Mechanisms underlying oxidative stress and ER stress

6.1. Endoplasmic reticulum stress and insulin resistance

In vitro, FFAs induce ER stress in adipocytes [32], hepatocytes [66], and pancreatic β-cells [39] resulting in the buildup of unfolded or misfolded proteins and UPR. Lipid infusion in heparinized rats not only increased the levels of FFAs in the plasma but also caused considerable ER stress in the liver [15]. This indicates that ER dysfunction is caused primarily due to systemic FFA overload. ER stress activates JNK, a kinase which phosphorylates the inhibitory serine residues on IRS and reduces insulin signaling [26,61]. ER stress and insulin resistance in diabetic (db/db) mice are alleviated by the overexpression of the protective ER chaperone, oxygen-regulated protein 150 (ORP150). This supports the hypothesis that ER stress acts as an inducing factor for insulin resistance.

7. Therapeutic implications: Targeting FFA-induced insulin resistance

The close causal relationship between high levels of FFAs and insulin resistance underscores the possibility of developing therapeutic interventions to reduce the levels of circulating FFAs. By altering their fate in cells or preventing their downstream lipotoxic effects, there could be a substantial improvement in the metabolic outcomes of T2DM. Experiments using human clamps and cell-based lipotoxicity models have revealed several intervention points that can be targeted.

7.1. Therapeutic strategies that reduce circulating FFA levels

The various therapeutic strategies developed for reducing levels of FFAs along with their mechanism are given in Table 2.

Acipimox inhibits lipolysis thereby reducing the levels of FFAs and increasing insulin sensitivity in the body [57]. This further supports the fact that reducing FFA levels reverses insulin resistance (Fig. 4).

TZDs are peroxisome proliferator-activated receptor gamma (PPARγ) agonists that increase the ability of adipocytes to store lipids and decrease the overflow of ectopic lipids leading to a decrease in plasma FFA levels. They increase insulin sensitivity in individuals with T2DM by reducing lipolysis and redistributing lipid deposition sites such that lipids are not deposited in skeletal muscle and liver [16]. Exercise training increases the oxidative capacity of mitochondria and enhances lipid management. Exercise has been shown to normalize DAG and JNK activity following lipid exposure and reverse experimentally-induced insulin resistance [23]. Circulating FFA levels are also reduced by dietary caloric restriction including decrease in saturated fats and increase in ω−3 PUFAs.

Albumin [1] acts as the primary carrier of free fatty acids in blood circulation and is involved in the regulation of the availability of FFAs in plasma as well as the transportation of lipids into tissues. Recent scientific data [3] have shown that the modification of albumin-FFA interaction can be used as a new approach to increasing insulin sensitivity. In experimental research, mice lacking albumin had a significant decrease in the levels of FFA in their blood circulation, reduction of ectopic lipid deposition, increased glucose tolerance, and improved insulin sensitivity even under obesogenic conditions. This suggests that albumin is not just a passive carrier of FFAs; it also plays a role in the metabolism of FFAs. Thus, the approach to manipulating albumin-mediated FFA transport, albumin-FFA interaction, and FFA traffic may be an interesting strategy for counteracting the effects of FFAs on insulin resistance [2].

7.2. Strategies that modify intracellular lipid partitioning

Lipid-driven insulin resistance in the muscle can be prevented by increasing the production of triglycerides through overexpression of DGAT1 to convert harmful DAG species into non-toxic TG droplets as demonstrated using transgenic mice [53]. This mechanism has not yet been translated into therapeutic intervention but this evidence demonstrates that intracellular lipid partitioning can be developed as a viable therapy. Monounsaturated fatty acids (MUFA), such as oleate (C18:1), prevent palmitate-induced toxicity, oxidative damage, and apoptosis of

Table 2
Therapeutic strategies for reducing the levels of circulating FFAs [HSL – hormone-sensitive lipase; FFA – free fatty acids; T2DM – type 2 diabetes mellitus; HMG-CoA - 3-Hydroxy−3-methylglutaryl-CoA; NAFLD – non-alcoholic fatty liver disease; PPARγ - peroxisome proliferator-activated receptor gamma; TG – triglycerides; FA – fatty acid; HFD – high-fat diet].

Drug / Class	Target / Mechanism	Studies / Trials	Characteristics	Reference
Nicotinic acid (Niacin)	Inhibits HSL in adipocytes via GPR109A receptor	Pilot human study (500 mg q1h suppressed FFA <0.2 mEq/L); animal models show acute lowering but rebound with chronic use	Acute potent FFA suppressor; flushing common side effect; rebound limits long-term use	[30]
Acipimox	Nicotinic acid analog; inhibits adipocyte lipolysis	Randomized crossover trial in metabolic syndrome (reduced FFA to normal levels, no endothelial benefit)	Short-term use (250 mg q6h for 7 days); studied in T2DM and metabolic syndrome	[4]
Statins (e.g., atorvastatin)	HMG-CoA reductase inhibition; indirect FFA reduction	Meta-analysis of 14 arms (19.42% FFA reduction)	Greater effect in longer trials (≥12 weeks); benefits in dyslipidemia and NAFLD	Sahebkar et al.
Thiazolidinediones (Pioglitazone)	PPARγ agonist; improves adipose insulin sensitivity	Long-term trial in T2DM (104 weeks; fasting FFA ↓0.08–0.11 mmol/L)	Reduces lipotoxicity; added to sulfonylurea/metformin	Roden et al.
Fibrates (Fenofibrate)	PPARα agonist; enhances adipose β-oxidation	Animal study in obese mice (lowered serum FFA); human study no FFA change but TG reduction	Primarily lowers TG; mixed FFA effects across species	[37]
Metformin	Inhibits hepatic gluconeogenesis; suppresses fasting lipolysis indirectly	Placebo-controlled study (day-long FFA ↓; fasting FFA lower in insulin-resistant subjects); clinical trial on hepatic FFA metabolism	Primarily lowers fasting FFA; no effect on stress-induced lipolysis; used in T2DM	[17]
Insulin therapy	Suppresses HSL via signaling; promotes FFA re-esterification	Sustained reduction trials (7 days; FFA ↓ improved insulin sensitivity in T2DM); hyperinsulinemic clamps	Standard in T2DM; reduces intramyocellular lipids; fasting/ postprandial effects	[9]
ω−3 Fatty Acids (e.g., Epanova)	Reduce TG synthesis; indirect FFA modulation	EVOLVE II trial (high TG patients; TG ↓ but FFA not primary); hypertriglyceridemia studies	Primarily TG-lowering; variable FFA impact; 2–4 g/day dosing	Kastelein et al.
Cannabidiol (CBD)	Inhibits de novo lipogenesis; alters FA metabolism	Animal studies (2-week HFD mice; intramuscular FFA ↓28%, specific FAs reduced)	Experimental; reduces lipid accumulation in muscle; potential in obesity	[11]

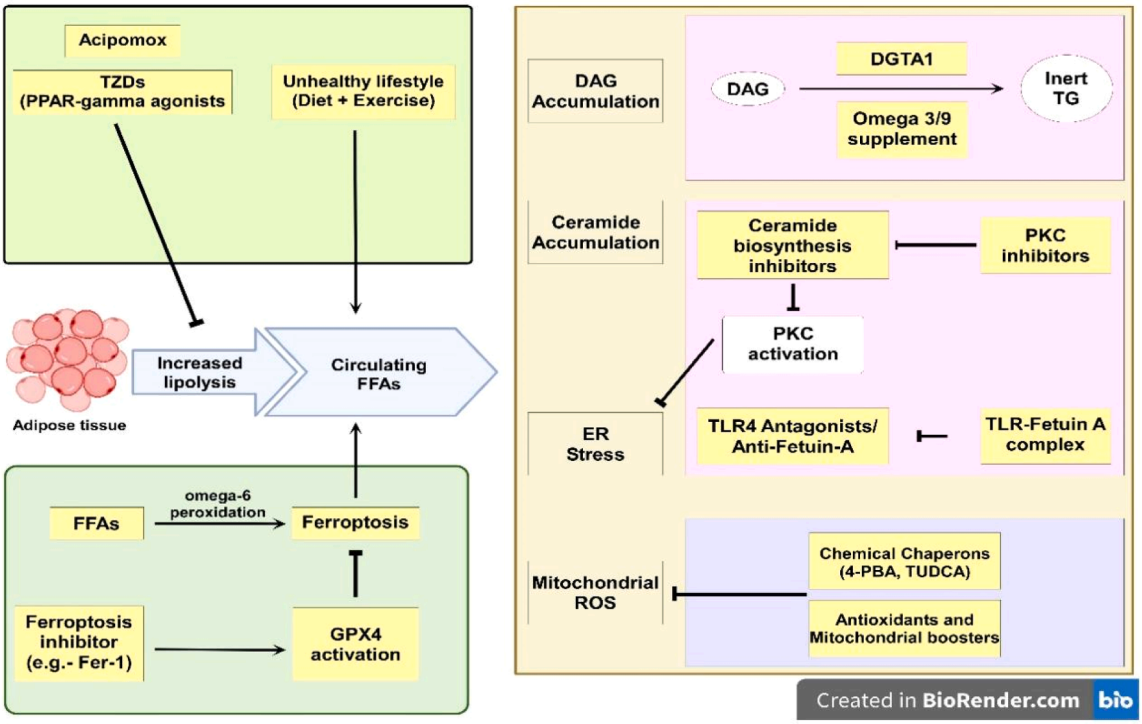


Fig. 4. Therapeutic mechanistics.

β-cells and muscle cells ([10]; Krummel et al., 2022). It was also found that ω−3 PUFAs can decrease inflammation, alter the membrane lipid composition, and possibly inhibit ceramide synthesis pathways [56].

7.3. Blocking lipotoxic signaling pathways

Table 3 gives a list of drugs that target different components of lipotoxic signaling pathways.

Increase in the levels of ceramide suppresses Akt signaling; blocking ceramide synthesis using serine palmitoyltransferase long chain base subunit 2 (Sptlc2) or myriocin in HFD models increased hepatic and muscular insulin sensitivity (Imierska et al., 2025). Therapies targeting de novo production of ceramides are currently being developed. PKCθ, PKCβ, and other novel isoforms of PKC that are mobilized by the action of DAG are key mediators of insulin resistance caused by FFA. Inhibition of certain PKC isoforms by pharmacologic or genetic treatments increased insulin signaling in HFD-fed rodents [55]. FFAs by themselves are weak activators of TLR4 but the presence of fetuin-A facilitates

Table 3
Therapeutic strategies for targeting various components of lipotoxic signaling pathways [TLR4 – toll-like receptor 4; PA – palmitic acid; HFD – high-fat diet; MAPK – mitogen-activated protein kinase; JNK – c-Jun N-terminal kinase; ERK – extracellular signal-regulated kinase; AST/CKMB – aspartate aminotransferase/creatine kinase-myocardial band; SFA – saturated fatty acid; MLK3/GSK−3 – mixed lineage kinase 3/glycogen synthase kinase−3; NASH – non-alcoholic steatohepatitis; S1P – sphingosine−1-phosphate; DGK – diacylglycerol kinase; DAG – diacylglycerol; FFA – free fatty acids].

Drug / Compound	Target / Mechanism	Studies / Trials	Characteristics	Reference
Salvianolic Acid A (SAA)	Inhibits TLR4/MyD88/MAPKs (JNK, ERK1/2)	HFD obese mice (reduced AST/CK-MB, cardiac damage); PA-treated H9c2 cells	Natural polyphenol from Salvia miltiorrhiza; anti-oxidant, cardioprotective	[68]
D-JNKi (peptide inhibitor)	JNK inhibitor	SFA hepatocytes (↓ lipoapoptosis); links to MLK3/GSK−3 in liver models	Blocks JNK-mediated cell death in NASH/obesity; improves insulin signaling	[35]
ABC294640	Sphingosine kinase 2 inhibitor	Phase I/II trials (cancer: glioblastoma, prostate cancer); preclinical ceramide elevation	Shifts ceramide/S1P for apoptosis induction; emerging in lipotoxic contexts	[63]
R59949/R50922	Diacylglycerol kinase (DGK) inhibitors	Huntington's cellular models (↓ mutant huntingtin toxicity via DAG signaling)	Modulates lipid second messengers; potential extension to FFA lipotoxicity	[69]

FFA-TLR4 interaction in adipocytes and macrophages. This results in NF-κB inflammation and insulin resistance [14]. The two promising approaches to inhibit FFA-induced inflammation and insulin resistance are to target TLR4 signaling and downregulate the expression of fetuin-A.

7.4. Reducing ER and oxidative stress

These agents have been shown to decrease ER stress and increase insulin sensitivity in several experimental models. They disrupt the ER stress - JNK activation - IRS−1 activity pathway [29] by stabilizing protein folding. ROS generation (for example, by using NADPH oxidase inhibitors) and increase in mitochondrial β-oxidation impair insulin signaling due to oxidative stress. The most effective physiological anti-oxidant therapy has been shown to be exercise as it induces biogenesis and clearance of lipid intermediates in the mitochondria [36].

7.5. Emerging frontiers: Ferroptosis and lipid peroxidation

While the current review mostly deals with insulin resistance, recent studies have shown that sustained levels of FFA can also cause β cell dysfunction via ferroptosis, thus aiding in the progression of insulin resistance to diabetes mellitus. According to recent studies on β-cells, ferroptosis caused by ω−6 PUFA is a lipotoxicity-related pathway [10]. β-cells can be protected by lipid peroxidation, pharmacological inhibition of ferroptosis by ferrostatin−1 (Fer−1), or GPX4 stimulation which is a new therapeutic approach and especially applicable in inflammatory diseases with fatty-acid-rich lesions.

7.6. Summary

Currently, successful therapeutic strategies for FFA-induced insulin resistance function through a combination of four mechanisms: reducing FFA availability (acipimox, TZDs, dietary control); redirecting lipid fluxes (DGAT1-mediated sequestration, oleate supplementation); blocking downstream lipotoxic pathways (ceramide synthesis inhibitors, TLR4/fetuin-A antagonists, PKC inhibitors); and mitigating cellular stress responses (chemical chaperones, antioxidants, ferroptosis inhibitors). Recent evidence regarding the above strategies have revealed that targeting insulin sensitivity and β-cell survival in T2DM can provide positive clinical outcomes at the systemic, cellular, and molecular levels by affecting FFA metabolism.

8. Future directions

Although there is remarkably strong evidence that links FFAs and insulin resistance, there remain multiple gaps regarding mechanisms and clinical translation. Addressing these disparities will involve investigating the causal role of lipid intermediates, enhancing therapeutic targeting, and personalizing interventions for individuals with T2DM. The areas of interest for future research are described below. Future research should aim at clarifying the role played by FFA-mediated insulin resistance and β-cell dysfunction in the development of type 2 diabetes mellitus.

8.1. Mechanistic and biological research priorities

Although the measurement of plasma FFA levels is extensively performed, it has recently been proposed that FFA flux, clearance rates, and tissue-specific lipid partitioning might have improved predictive accuracy for metabolic dysfunction compared to static FFA levels [57]. Future work should include measurement of dynamic FFA turnover in organs in the context of muscular, ganglial, and fat tissue uptake; establishment of the effect of changes in lipid clearance on ectopic lipid storage, accumulation of DAG and ceramides, and downstream insulin resistance; and use of high-resolution stable isotopes, lipidomics, and tracer-based metabolic flux measures.

All FFAs do not cause insulin resistance. Saturated fatty acids (e.g., palmitate) induce lipotoxicity, whereas MUFAs (e.g., oleate) prevent lipotoxicity ([10]; Krummel et al., 2022). Future work should determine which compounds (DAG or ceramides) are most toxic to insulin signaling, the possibility of clearing lipids through metabolism and consuming 'good' lipids (MUFAs, ω−3 PUFAs), and the molecular differences between lipotoxic and lipoprotective lipid profiles in humans.

The negative effects of FFAs are unevenly distributed among the tissues whereas β-cells, hepatocytes, and skeletal muscles are different in their vulnerability. Future work should carry out longitudinal examinations of the progression of muscle DAG, hepatic ceramides, and β-cell ferroptosis in early stages of insulin resistance; map the time period of lipotoxic events across early and late stages to find out which mechanisms are primary or secondary contributors of the progression of T2DM; and determine the molecular switch points at which insulin resistance is converted from reversible to irreversible.

Although DAG-mediated PKC activation, ER stress, and oxidative stress have been proved to result in lipotoxicity, a number of gaps remain in our understanding. These gaps include: which PKC isoforms predominantly mediate insulin resistance and do the isoforms vary between tissues [55], what are the mechanisms of ER stress through which Sptlc2 promotes ceramide generation and is it possible to safely regulate this pathway [29], and how does ferroptosis contribute to β-cell failure caused by increased levels of ω−6 PUFA compared with apoptosis and necrosis [8,10]. These questions can be answered using advanced multimodal omics and imaging.

Further research is also required to explore the role of albumin-mediated FFA transportation in metabolic abnormalities. It has been established by some recent experiments that albumin deficiency leads to changes in systemic FFA transport, reduced FFA levels in the blood, and enhanced insulin sensitivity, thus, emphasizing the importance of albumin-FFA interaction in terms of lipid flux.

8.2. Translational and therapeutic opportunities

Reducing FFA levels can partially attenuate insulin sensitivity. Other therapeutic interventions can target the downstream lipid pathways, for example, selectively blocking ceramide synthesis in the absence of changes in lipid metabolism throughout the body [62,67], and use of antagonistic lectin receptor for fetuin-A to target the FFA-inflammation axis [14], mitochondrial and ROS antioxidants, anti-β-cell ferroptosis inhibitors (Fer−1, GPX4 agonists) [8,10], specific PKC inhibitors based on isoform selectivity and tissue localization, and multi-lipotoxic node combination therapy rather than agents that target a single node in a pathway.

Individuals respond differently to increased FFA levels. Precision medicine interventions are required to categorize patients based on lipidomic markers (DAG), spillovers and rates of adipose tissue lipolysis, mitochondrial efficiency of muscles, inflammatory markers such as fetuin-A and TLR4 [34], and sensitivity to β-cell ferroptosis. This information might inform more focused interventions which may comprise dietary changes, pharmacotherapies to reduce lipids, and molecular inhibitors.

8.3. Emerging technologies to advance lipotoxicity research

These include single-cell lipidomics to map patterns of lipid damage based on cell-type, CRISPR gene editing to uncover lipid metabolism regulation networks (DGAT1, Sptlc2, GPX4), simulating chronic lipotoxicity in organ-on-chip and microfluidic β-cell models, and prediction of progression of lipotoxicity and therapeutic response using artificial intelligence-based metabolic modeling.

9. Conclusion

Increased levels of FFAs are central and causal in the development of insulin resistance and the course of T2DM. Human clamp-based, animal, and in vitro lipotoxicity experiments have provided insights into the effects on insulin action due to increased FFA levels via multiple convergent mechanisms such as accumulation of lipid intermediates such as DAG and ceramide, activation of new protein kinase C (PKC) isoforms, ER stress, oxidative stress, inflammation, and ferroptosis of β-cells. These mechanisms disrupt insulin signaling by exerting their effects on IRS−1, PI3K-Akt axis, and GLUT4 translocation resulting in systemic metabolic dysfunction.

Notably, all fatty acids do not exert equal biological effects. Saturated fatty acids, especially palmitate, are highly lipotoxic whereas MUFAs such as oleate can result in the formation of harmless triglycerides that can be stored and guard against cellular stress. This highlights the importance of measuring effective total FFA content to identify lipid species-specific functions, flux, and specific organ vulnerability.

Cytotherapeutic interventions that lower the levels of circulating FFAs by enhancing intracellular lipid metabolism and inhibiting downstream lipotoxic signaling have been shown to have great potential. Drugs that reduce FFA levels (e.g., acipimox), insulin sensitizers (e.g., TZDs), exercise, and dietary measures have been shown to enhance insulin sensitivity. PKC isoforms, ceramide synthesis, TLR4-fetuin-A signaling, ER stress, and ferroptosis are newly identified mechanisms that that have high clinical translation potential. Finally, systemic decrease in FFA levels in conjunction with local inhibition of lipotoxic pathways might be a promising approach. The present review underscores the importance of FFAs in the development of insulin resistance, but at the same time it acknowledges that the lipotoxic effect might adversely influence pancreatic β-cell function and viability.

CRediT authorship contribution statement

Chakraborty Dr. Indrani: Supervision. **Manik Prof. Dr. Nabin Baran:** Validation. **Gautam Dr. Arunodaya:** Validation. **Subhajit Ghosh:** Visualization. **Maity Dr. Subhajit:** Writing – original draft, Visualization, Formal analysis, Conceptualization. **Swati Banerjee:** Writing – original draft, Visualization, Formal analysis, Conceptualization.

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Declaration of Competing Interest

None.

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