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Review

Dysregulated Skeletal Muscle Lipid Handling Drives Myocardial Mitochondrial Dysfunction Through ASK-1 and PPARγ Signaling

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Abstract

Cardiovascular disease is the leading cause of mortality in insulin-resistant individuals, with metabolic cardiomyopathy preceding overt heart failure in a substantial proportion of patients with diabetes. Skeletal muscle accounts for approximately 40% of body mass and nearly 80% of insulin-stimulated glucose disposal, positioning it as a major determinant of systemic lipid flux. Dysregulation of lipid droplet dynamics, lipolysis, and fatty acid trafficking in skeletal muscle alters circulating lipid availability and promotes ectopic lipid deposition and mitochondrial stress in the myocardium. Intramyocellular lipid handling is governed by coordinated actions of lipid droplets, perilipin proteins (PLIN2 and PLIN3), adipose triglyceride lipase (ATGL), and diacylglycerol acyltransferases (DGAT1/2), which together regulate the rate and composition of fatty acid release into the circulation. Impaired coupling between intramyocellular lipid droplet turnover and mitochondrial oxidation in insulin-resistant muscle increases circulating free fatty acids, reducing cardiac oxidative capacity. In response, the myocardium undergoes mitochondrial lipid remodeling, including alterations in cardiolipin composition that impair cristae structure and electron transport chain efficiency. Excess lipid exposure activates apoptosis signal-regulating kinase-1 (ASK-1), promoting cardiomyocyte apoptosis and inflammatory signaling, while peroxisome proliferator-activated receptor gamma (PPARγ) modulates lipid uptake, storage, and mitochondrial oxidation in a context-dependent manner. This review integrates skeletal muscle–cardiac lipid crosstalk with ASK-1 and PPARγ signaling to define mechanisms linking peripheral insulin resistance to early myocardial dysfunction and to identify targets for intervention before irreversible cardiac remodeling develops.

Keywords: metabolic cardiomyopathy; myocardial lipotoxicity; insulin resistance; mitochondrial dysfunction; inter-organ lipid signaling; cardiac metabolic remodeling

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1. Introduction

Insulin resistance precedes type 2 diabetes and is an emerging risk factor for cardiovascular disease with approximately 25% of the U.S. population having clinically significant insulin resistance [1,2]. The relationship between insulin resistance and cardiovascular complications involves alterations in systemic lipid metabolism, ectopic lipid accumulation, and perturbations in cellular energy homeostasis. Skeletal muscle, accounting for approximately 40% of body mass and serving as the primary site of insulin-stimulated glucose disposal, plays an important role in regulating circulating lipid availability [3]. Impaired

insulin signaling in skeletal muscle alters lipid droplet dynamics, disrupts lipolysis, and modulates fatty acid oxidation capacity, leading to increased systemic lipid flux [4]. This metabolic dysregulation affects the myocardium, which relies predominantly on fatty acid oxidation for energy production and is therefore vulnerable to lipid overload [5]. Excess lipid delivery to the heart, coupled with impaired mitochondrial oxidative capacity, results in ectopic lipid accumulation within cardiomyocytes [6]. This lipid excess triggers mitochondrial dysfunction, oxidative stress, and activation of stress-responsive signaling pathways, leading to contractile dysfunction and structural remodeling.

The molecular mechanisms linking peripheral insulin resistance to cardiac lipotoxicity involve coordinated changes in lipid transport, storage, and oxidation [6]. CD36, a multifunctional glycoprotein and the predominant cardiac fatty acid transporter, becomes dysregulated in insulin-resistant states [7]. In an insulin-resistant state, CD36 becomes localized to the plasma membrane, resulting in an unregulated fatty acid influx that exceeds the myocardium's oxidative and storage capacity [8], resulting in metabolic inflexibility and converting fatty acids from essential fuel substrates into lipotoxic intermediates that impair cellular function.

Apoptosis signal-regulating kinase 1 (ASK-1) is an important mediator of lipid-induced cardiac stress [9]. As a member of the MAP3K family, ASK-1 is activated by reactive oxygen species and endoplasmic reticulum stress, two defining features of myocardial lipotoxic injury. Once activated, ASK-1 initiates downstream signaling cascades involving p38 MAPK and JNK pathways that promote cardiomyocyte apoptosis, inflammation, and fibrosis [10]. Evidence from knockout models identifies ASK-1 as a key contributor to metabolic cardiomyopathy, as genetic loss of ASK-1 prevents diet-induced cardiac dysfunction, maintains contractile function, and reduces myocardial inflammation [11]. In parallel, peroxisome proliferator-activated receptor gamma (PPARγ) provides transcriptional control of lipid metabolism in both skeletal muscle and cardiac tissue [12]. PPARγ regulates the genes involved in fatty acid uptake, lipid storage, and mitochondrial oxidation, enabling cells to adapt to varying lipid loads while preventing accumulation of lipotoxic intermediates [13].

These findings support a sequential mechanistic link in which lipid dysregulation originating in insulin-resistant skeletal muscle increases lipid delivery to the heart, imposing sustained oxidative and energetic stress on myocardial mitochondria. When lipid uptake exceeds mitochondrial oxidative capacity, cardiomyocytes experience stress conditions that favor activation of stress-sensitive kinases such as ASK-1, while simultaneously disrupting PPARγ-dependent transcriptional control of lipid handling [14]. This convergence of mitochondrial stress signaling and altered nuclear regulation provides a mechanistic framework connecting peripheral insulin resistance to myocardial lipotoxic injury.

The interplay between skeletal muscle lipid handling and cardiac lipid metabolism, thus represents more than simple substrate overflow. Skeletal muscle releases not only free fatty acids but also lipid-laden exosomes and myokines that modulate distant tissue metabolism. These secreted factors carry lipid species, microRNAs, and signaling proteins that influence cardiac gene expression, mitochondrial function, and inflammatory responses [15]. In insulin-resistant states, the composition and function of these muscle-derived factors are altered, contributing to cardiac metabolic dysfunction through mechanisms independent of circulating free fatty acid levels [16].

Despite recognition of these individual mechanisms, a major gap is how peripheral insulin resistance, within skeletal muscle, contributes to sustained myocardial lipid stress and downstream cardiac injury. In this review, we illustrated how disruptions in skeletal muscle lipid droplet dynamics, lipolysis, and mitochondrial fatty acid oxidation increase lipid delivery to the heart. We highlighted the mechanisms by which myocardial mito-

chondrial remodeling and ASK-1 activation mediate the cardiac response to lipid overload, and how PPARγ signaling coordinates lipid handling between skeletal muscle and cardiac tissue. By focusing on these inter-tissue pathways, the article defines early events in metabolic cardiomyopathy and identifies the points where an early intervention may prevent progression to irreversible cardiac remodeling.

2. Methodology

We conducted a systematic search using PubMed with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to examine the mechanisms linking dysregulated skeletal muscle lipid handling to myocardial mitochondrial dysfunction through ASK-1 and PPARγ signaling pathways.

2.1. Search Strategy

A comprehensive literature search was performed across databases, including PubMed, covering studies published between 2000 and 2025, yielding a total of 1733 records. The search strategy employed both Medical Subject Headings (MeSH) terms and free-text keywords to ensure broad coverage of relevant mechanistic, preclinical, and clinical studies. The primary search terms included:

- "Skeletal muscle AND lipid metabolism AND cardiac dysfunction" (n = 312 studies);
- "Metabolic cardiomyopathy AND insulin resistance" (n = 1134 studies);
- "Insulin resistance AND myocardial lipotoxicity" (n = 130 studies);
- "Intramyocellular lipid AND cardiomyopathy" (n = 7 studies);
- "Skeletal muscle lipolysis AND heart failure" (n = 13 studies);
- "Skeletal muscle AND Lipid metabolism AND PPARγ Signaling" (n = 137 studies).

2.2. Study Selection and Inclusion Criteria

The search was refined to include only studies published between 1 January 2000, and 1 January 2025, focusing exclusively on peer-reviewed articles in indexed journals. After removing duplicates, 133 studies were identified as linking skeletal muscle, lipid metabolism and cardiomyopathy. Screening was conducted based on titles and abstracts, leading to the exclusion of 92 studies due to irrelevance. A full-text review of the remaining 41 articles was then performed, resulting in the exclusion of additional studies for the following reasons:

- Irrelevant outcomes (n = 92 studies).

Ultimately, 41 studies met the inclusion criteria and were selected for analysis (Supplementary Figure S1).

3. Skeletal Muscle Lipid Handling as an Upstream Determinant of Systemic Lipid Flux

Skeletal muscle is the primary site of postprandial fatty acid uptake and a major regulator of lipid disposal. In insulin-resistant conditions, an imbalance in muscle lipid storage and oxidation alters the balance between intracellular lipid retention and fatty acid release. These changes led to skeletal muscle as a potential upstream source of sustained lipid oversupply to peripheral organs, including the myocardium [3]. The following sections examine the molecular mechanisms governing lipid droplet dynamics, lipolysis, and mitochondrial fatty acid oxidation in skeletal muscle and their relevance to systemic lipid redistribution. The principal molecular regulators coordinating lipid droplet stability, intracellular lipolysis, fatty acid trafficking, and mitochondrial oxidation in skeletal muscle are summarized in Table 1.

Table 1. Key Molecular Regulators of Skeletal Muscle Lipid Handling.

Protein	Cellular Location	Primary Function	Effect in Insulin Resistance	Key References
PLIN2 (ADRP)	Lipid droplet surface (cytosolic face)	Stabilizes lipid droplets, limits basal lipolysis, buffers fatty acids to prevent accumulation of lipotoxic intermediates.	Upregulated in insulin resistance, protects against acute lipotoxicity while enabling chronic lipid overload.	[17]
PLIN3 (TIP47)	Lipid droplets, cytosol and ER–lipid droplet contact sites	Facilitates lipid droplet biogenesis, trafficking, and turnover.	Altered localization and function in insulin resistance, may enhance lipid trafficking toward circulation rather than oxidation.	[18]
ATGL (PNPLA2)	Lipid droplets	Rate-limiting enzyme of intracellular triglyceride hydrolysis and releases fatty acids for oxidation.	Lipolysis becomes uncoupled from mitochondrial oxidation. Excess FA release promotes DAG/ceramide accumulation and FA spillover into circulation.	[19]
CGI-58 (ABHD5)	Lipid droplet surface	Co-activator of ATGL and amplifies triglyceride hydrolysis.	Dysregulated activation enhances lipolysis without matched oxidative capacity, exacerbating lipid-induced insulin resistance.	[20]
DGAT1/ DGAT2	ER (DGAT1), ER–lipid droplet interface (DGAT2)	Catalyze final step of triglyceride synthesis, promote safe lipid storage.	DGAT1 protects against lipotoxicity by diverting FA into neutral storage.	[21]
CD36 (FAT)	Sarcolemma, endosomes and mitochondria-associated membranes	Mediates fatty acid uptake and intracellular trafficking to mitochondria.	Increased expression and sarcolemma trapping enhance FA influx beyond oxidative capacity, contributing to systemic lipid oversupply.	[22]
CPT1	Outer mitochondrial membrane	Controls mitochondrial fatty acid entry and β-oxidation.	Functional limitation due to mitochondrial defects leads to incomplete FA oxidation and acylcarnitine accumulation.	[23]
PPARγ	Nucleus	Transcriptional regulator coordinating fatty acid uptake, lipid droplet formation and mitochondrial oxidation.	Reduced expression or impaired activity limits adaptive lipid buffering and oxidation, exacerbating lipotoxic stress and fatty acid spillover to peripheral organs.	[24]

3.1. Lipid Droplet Formation and Regulation

Intramyocellular lipid droplets serve as dynamic repositories for fatty acids, buffering against lipotoxic intermediates while providing readily accessible energy substrates [25]. These organelles consist of a neutral lipid core, primarily composed of triacylglycerols and sterol esters, surrounded by a phospholipid monolayer decorated with structural and regulatory proteins. The perilipin family of proteins, particularly PLIN2 (adipose differentiation-related protein, ADRP) and PLIN3 (tail-interacting protein of 47 kDa, TIP47), coat the lipid droplet surface and regulate access of lipases to the stored lipids [26].

PLIN2 is constitutively expressed in skeletal muscle and plays a protective role by limiting basal lipolysis and preventing excessive fatty acid release [27]. Studies in PLIN2 knockout mice have demonstrated increased basal fatty acid oxidation and improved insulin sensitivity, suggesting that PLIN2-mediated lipid sequestration can, under certain conditions, contribute to metabolic inflexibility [28]. However, PLIN2 also protects against lipotoxicity by preventing the accumulation of bioactive lipid intermediates such as diacylglycerols and ceramides. PLIN3, which exhibits lower affinity for lipid droplets compared

to PLIN2, is thought to facilitate lipid droplet biogenesis and lipid trafficking between cellular compartments [29].

The formation of lipid droplets requires the coordinated action of several enzymatic systems. Diacylglycerol acyltransferases (DGAT1 and DGAT2) catalyze the final step of triacylglycerol synthesis, converting diacylglycerol and fatty acyl-CoA to triacylglycerol. DGAT1 is localized primarily to the endoplasmic reticulum, while DGAT2 is found at sites of lipid droplet formation. Both these enzymes play distinct roles in lipid metabolism, with DGAT1 being important for maintaining lipid homeostasis under steady-state conditions, whereas DGAT2 becomes critical during periods of lipid excess [30]. Overexpression of DGAT1 in skeletal muscle protects against diet-induced insulin resistance by channeling fatty acids into neutral lipid storage rather than allowing accumulation of lipotoxic intermediates [31].

Among these lipotoxic intermediates, ceramides represent particularly potent bioactive signaling molecules that actively drive cellular dysfunction beyond simple lipid overload. When lipolysis exceeds oxidative capacity, the resulting accumulation of diacylglycerols serves as substrate for de novo ceramide synthesis via ceramide synthase (CerS) enzymes. Different CerS isoforms generate ceramides with distinct acyl chain lengths, such as CerS1, which produces C18-ceramide, CerS2 produces very-long-chain ceramides (C22-C24), while CerS5 and CerS6 generate C16-ceramide [32]. In insulin-resistant muscle, C16-ceramide and C18-ceramide accumulate preferentially, species that are particularly cytotoxic and correlate with insulin resistance severity [33]. Ceramides activate ASK-1 through three convergent mechanisms that create a sustained stress signal. Complex III inhibition generates superoxide that oxidizes thioredoxin and releases ASK-1 from its inhibitory complex [34]. Ceramides also activate protein phosphatase 2A (PP2A), which removes inhibitory phosphate groups from ASK-1 and maintains it in an active state [35]. Additionally, ceramides disrupt ER calcium homeostasis and trigger ER stress, activating the unfolded protein response and its downstream effector ASK-1. Among ceramide species, C16:0-ceramide demonstrates the most potent ASK-1 activation, which explains its strong correlation with adverse cardiac outcomes [36]. This mechanism extends beyond cardiomyocyte-generated ceramides. Cardiomyocytes actively take up these circulating ceramides, where they exert direct cardiotoxic effects. This establishes a distinct muscle–heart signaling axis whereby skeletal muscle exports bioactive lipid mediators that directly activate cardiac stress pathways independent of free fatty acid delivery.

3.2. ATGL-Mediated Lipolysis and Fatty Acid Release

Adipose triglyceride lipase (ATGL), also known as patatin-like phospholipase domain-containing protein 2 (PNPLA2), catalyzes the rate-limiting step of intracellular lipolysis by hydrolyzing triacylglycerol to diacylglycerol. In skeletal muscle, ATGL activity is regulated by comparative gene identification-58 (CGI-58), a coactivator that enhances ATGL enzymatic activity, and G0/G1 switch gene 2 (G0S2), an inhibitor that suppresses lipolysis [37]. The balance between ATGL activation and inhibition determines the rate of fatty acid release from intramyocellular lipid droplets.

In insulin-sensitive individuals, ATGL-mediated lipolysis is tightly coupled to fatty acid oxidation, ensuring that released fatty acids are efficiently consumed by mitochondria [38]. This coupling prevents accumulation of diacylglycerols and ceramides, lipid intermediates that interfere with insulin signaling through activation of protein kinase C isoforms and inhibition of Akt phosphorylation. In insulin-resistant states, however, this coupling is disrupted [39]. ATGL-mediated lipolysis proceeds, but mitochondrial oxidative capacity is insufficient to handle the fatty acid load, resulting in accumulation of lipotoxic intermediates within myocytes and increased fatty acid efflux into circulation [40].

The role of skeletal muscle lipolysis in systemic lipid homeostasis remains incompletely understood. While adipose tissue is the primary source of circulating free fatty acids during fasting and exercise, skeletal muscle lipolysis contributes to local fatty acid availability and may influence whole-body lipid partitioning. Studies using stable isotope tracers have demonstrated that intramyocellular lipid turnover is substantial, with complete replacement of lipid droplet contents occurring over several days [41]. This suggests that skeletal muscle actively participates in lipid trafficking and the dysregulation of muscle lipolysis leads to systemic metabolic consequences.

3.3. Mitochondrial Fatty Acid Oxidation and CD36-Mediated Uptake

Fatty acids released from lipid droplets are transported into mitochondria for β-oxidation. This process requires carnitine palmitoyltransferase 1 (CPT1), which catalyzes the formation of acylcarnitines that can traverse the mitochondrial membranes via the carnitine-acylcarnitine translocase. Once inside the mitochondrial matrix, fatty acids undergo β-oxidation, generating acetyl-CoA that enters the tricarboxylic acid cycle and reducing equivalents (NADH and FADH2) that feed into the electron transport chain [42].

CD36 plays a dual role in skeletal muscle, mediating both sarcolemmal fatty acid uptake and intracellular fatty acid trafficking to mitochondria [7]. At the plasma membrane, CD36 facilitates fatty acid transport across the lipid bilayer, in coordination with fatty acid transport proteins (FATPs) and fatty acid binding proteins (FABPs) to shuttle fatty acids from the extracellular space into the cytoplasm [43]. Within the cell, CD36 interacts with mitochondrial membranes, potentially facilitating fatty acid delivery to CPT1 for mitochondrial uptake. In insulin-sensitive muscle, CD36 expression and subcellular localization are dynamically regulated, with insulin promoting CD36 translocation to the sarcolemma during fed states and its internalization during fasting [44].

Mitochondrial oxidative capacity in skeletal muscle is determined by mitochondrial content, intrinsic respiratory function, and substrate availability [45]. In insulin-resistant individuals, numerous studies have documented reductions in mitochondrial density and impaired oxidative phosphorylation capacity [46,47]. Whether these mitochondrial defects are primary causes or secondary consequences of insulin resistance remains unknown. Regardless of causality, reduced mitochondrial oxidative capacity creates a mismatch between lipid delivery and lipid oxidation, favoring accumulation of incompletely oxidized fatty acid intermediates.

Incomplete fatty acid oxidation generates acylcarnitine species that accumulate in muscle and spill over into circulation [48]. These acylcarnitines serve as biomarkers of metabolic stress, reflecting the inability of mitochondria to fully oxidize fatty acids. Long-chain acylcarnitines, are associated with insulin resistance and cardiovascular disease risk [49]. The accumulation of these intermediates may contribute to mitochondrial dysfunction by interfering with adenine nucleotide translocase function and disrupting mitochondrial membrane integrity.

Endurance trained individuals differ fundamentally from this pathological state despite sustaining high intramyocellular lipid content that often exceeds levels observed in insulin resistant individuals they maintain preserved insulin sensitivity through tight coupling of lipid mobilization with mitochondrial fatty acid oxidation [50]. This “athlete’s paradox” reflects enhanced mitochondrial density, increased oxidative enzyme activity, improved insulin-stimulated CD36 translocation, and upregulated capacity for lipid droplet remodeling [51]. Training adaptations preserve metabolic flexibility by matching fatty acid release to oxidative demand, preventing spillover of lipotoxic intermediates despite high lipid turnover rates. Studies comparing sedentary insulin-resistant subjects with endurance athletes show that exercise training recouples ATGL-mediated lipolysis with mitochon-

drial consumption, normalizing circulating fatty acid profiles and reducing ectopic lipid deposition in distant organs including the heart [52].

3.4. PPARγ Regulation of Skeletal Muscle Lipid Metabolism

PPARγ is a nuclear receptor best known for its role in adipocyte differentiation and lipid storage, but it also regulates lipid metabolism in skeletal muscle [53]. PPARγ activation by endogenous ligands such as oxidized fatty acids or synthetic agonists such as thiazolidinediones induces expression of genes involved in fatty acid uptake (CD36, fatty acid transport proteins), lipid storage (PLIN2, DGAT1/2), and fatty acid oxidation (CPT1, acyl-CoA dehydrogenases) [54]. This coordinated transcriptional response enhances metabolic flexibility by increasing the muscle's capacity to handle lipid loads.

The therapeutic effects of thiazolidinediones on insulin sensitivity are mediated, through PPARγ activation in skeletal muscle [55]. These compounds promote lipid storage in adipose tissue, reducing circulating free fatty acid levels, and enhance lipid buffering capacity in muscle. However, PPARγ activation also has direct effects on muscle metabolism, improving mitochondrial function and reducing lipotoxic stress [56]. Studies in muscle-specific PPARγ knockout mice have demonstrated impaired insulin sensitivity and increased susceptibility to diet-induced metabolic dysfunction, showing the importance of muscle PPARγ signaling in metabolic homeostasis [57].

In insulin-resistant states, PPARγ expression and activity in skeletal muscle are often reduced. This impairment diminishes the muscle's adaptive capacity to manage lipid excess, exacerbating lipotoxicity and contributing to systemic metabolic dysfunction [58]. Restoring PPARγ function through pharmacological or lifestyle interventions may therefore represent a viable strategy for improving both skeletal muscle and systemic lipid metabolism.

3.5. Epigenetic Control of Skeletal Muscle Lipid Metabolism

Beyond transcriptional regulation, the expression of genes governing lipid handling in skeletal muscle is controlled by epigenetic modifications that establish persistent patterns of metabolic dysfunction in insulin resistance, which is associated with altered histone acetylation at promoters and enhancers governing of fatty acid transport, lipid droplet turnover, and mitochondrial oxidation, including CD36, PLIN2, ATGL, and CPT1 [59]. Increased activity of class I and II histone deacetylases, particularly HDAC3 and HDAC5, suppresses oxidative gene networks, coordinated by PPARγ and PGC-1α, thereby limiting adaptive upregulation of fatty acid oxidation in presence of lipid excess and favoring intramyocellular lipid retention and spillover [60].

DNA methylation provides an additional layer of regulation that stabilizes this maladaptive phenotype. Hypermethylation at regulatory elements proximal to PPAR response motifs has been linked to reduced inducibility of lipid oxidation genes, attenuating transcriptional responsiveness even when PPARγ signaling is pharmacologically engaged. Concurrent hypomethylation at stress- and inflammation-associated loci may further amplify lipid-induced redox and cytokine signaling, reinforcing insulin resistance and mitochondrial stress [61].

Chromatin remodeling complexes that control nucleosome positioning at metabolic gene enhancers are also disrupted in insulin-resistant muscle. The SWI/SNF complex, which normally facilitates access of transcription factors to target genes, shows reduced activity at PPARγ and PGC-1α binding sites [62]. This impairs the coordinated induction of lipid-handling programs even when transcription factors are present and activated. Recent studies demonstrate that exercise training partially reverses these epigenetic marks, increasing histone acetylation at oxidative gene promoters and restoring chromatin accessibility [63]. This epigenetic remodeling contributes to the sustained improvements

in insulin sensitivity observed with regular physical activity, extending beyond acute metabolic effects.

The persistence of epigenetic modifications explains that, once insulin resistance is established, it is difficult to reverse through short-term interventions. Lipid-induced alterations in the epigenetic sphere create stable patterns of gene expression that preserve the metabolic dysfunction even after acute lipid overload is corrected. Targeting epigenetic enzymes through HDAC inhibitors or DNA methyltransferase modulators represents a potential therapeutic strategy to reset chromatin states and restore adaptive lipid handling capacity in skeletal muscle.

4. Regulation of Cardiac Lipid Uptake and Metabolic Remodeling

Dysregulated skeletal muscle lipid content increases fatty acids to peripheral tissues [64]. The myocardium receives this lipid burden through both direct uptake of circulating free fatty acids and incorporation of triglyceride-rich lipoproteins released by the liver in response to elevated systemic lipid flux. The impaired lipid droplet turnover, uncoupled ATGL-mediated lipolysis, reduced mitochondrial oxidative capacity, and disrupted PPARγ signaling in insulin-resistant skeletal muscle drive sustained elevation of circulating fatty acids and qualitative changes in muscle-derived secreted factors. These changes impose a sustained metabolic burden on the myocardium [65]. The myocardium is continuously exposed to circulating lipid substrates and relies on coordinated coupling of fatty acid uptake to mitochondrial oxidative capacity to sustain contractile function [66]. During systemic lipid oversupply, this coupling is dysregulated, leading to disproportionate lipid entry relative to oxidative capacity [67]. Persistent lipid excess initiates metabolic remodeling characterized by altered substrate utilization, intracellular lipid accumulation, and mitochondrial stress [68]. This section examines the mechanisms governing myocardial fatty acid uptake, lipid storage, and downstream signaling pathways that link lipid overload to early cardiomyocyte dysfunction.

4.1. Myocardial Fatty Acid Uptake and Storage

The heart exhibits metabolic flexibility, oxidizing glucose, fatty acids, lactate, ketones, and amino acids to meet its energy demands. Under normal physiological conditions, fatty acids provide 60–90% of the heart's energy needs, with glucose contributing the remainder [69]. This metabolic profile reflects the heart's high energetic demands and the efficiency of fatty acid oxidation in generating ATP.

Fatty acid uptake by cardiomyocytes is mediated by several transport proteins, with CD36 (fatty acid translocase) playing the dominant role [70]. Beyond cardiac tissue, CD36 functions as a central regulator of systemic lipid partitioning, linking obesity, dyslipidemia, and ectopic lipid deposition across organs, thereby amplifying lipid oversupply to metabolically active tissues [71]. CD36 is located both on the sarcolemma and in intracellular vesicles, and its translocation to the cell surface is regulated by insulin signaling and metabolic stimuli. In insulin-resistant states, CD36 expression is increased, and the protein becomes constitutively localized to the sarcolemma, resulting in excessive fatty acid uptake that exceeds oxidative capacity [22]. This imbalance leads to the accumulation of intracellular lipids within cardiomyocytes.

Like skeletal muscle, the heart forms lipid droplets to store excess fatty acids and protect against lipotoxic stress [72]. However, the heart has a limited capacity for lipid storage compared to muscle or adipose tissue. When lipid delivery exceeds both oxidative capacity and storage capacity, lipotoxic intermediates accumulate. Diacylglycerols activate protein kinase C isoforms that impair insulin signaling and promote hypertrophic remodeling. Ceramides induce cardiomyocyte apoptosis through mitochondrial dysfunction

and activation of death signaling pathways [39]. When insulin-resistant skeletal muscle delivers fatty acids faster than the heart can oxidize or store them, cardiomyocyte mitochondria undergo membrane remodeling in response to chronic lipid exposure. This remodeling depletes cardiolipin and alters its composition, disrupting the cristae structure essential for efficient respiratory function and progressively impairing the mitochondria's energy-producing capacity.

4.2. Mitochondrial Lipid Remodeling and Cardiolipin Dynamics

Cardiac mitochondria are not merely sites of fatty acid oxidation but undergo structural and compositional remodeling in response to metabolic stress [73]. Cardiolipin, a unique phospholipid found exclusively in the inner mitochondrial membrane, is essential for maintaining cristae architecture and organizing respiratory chain super complexes [74]. The fatty acid composition of cardiolipin influences membrane fluidity, protein-lipid interactions, and susceptibility to oxidative damage.

In insulin-resistant and diabetic hearts, cardiolipin content is reduced, and its fatty acid composition is altered, with decreased linoleic acid content being a consistent finding [75]. This mitochondrial lipid remodeling represents Layer 3 of the cardiac stress cascade depicted in Figure 1, where mitochondrial adaptive capacity buffers against lipid excess until overwhelmed by sustained exposure. These changes impair respiratory chain function, reduce ATP synthesis efficiency, and increase reactive oxygen species production. Cardiolipin peroxidation, catalyzed by cytochrome c, triggers the release of pro-apoptotic factors from mitochondria, initiating the intrinsic apoptotic pathway [76]. Cardiolipin peroxidation initiates a cascade of lipid peroxidation reactions within mitochondrial membranes, generating reactive aldehydes including 4-hydroxynonenal (4-HNE), malondialdehyde (MDA), and acrolein [77]. The 4-HNE modification irreversibly inactivates key metabolic enzymes and antioxidant proteins. In lipid-overloaded cardiomyocytes, 4-HNE accumulation reaches pathological levels, modifying critical proteins including mitochondrial aldehyde dehydrogenase 2 (ALDH2), which normally detoxifies reactive aldehydes, creating a feed-forward cycle of oxidative damage [78]. The irreversibility of these protein modifications distinguishes lipid peroxidation from other forms of oxidative stress and represents a critical transition point from adaptive metabolic remodeling to fixed cellular damage.

Mitochondrial fatty acid oxidation in the heart is regulated at multiple levels, including substrate availability, transport into mitochondria, and enzymatic capacity [79]. Malonyl-CoA, produced by acetyl-CoA carboxylase, is a potent inhibitor of CPT1 and serves as a metabolic switch between fatty acid synthesis and oxidation [80]. In insulin-resistant hearts, malonyl-CoA levels are often reduced due to increased AMP-activated protein kinase (AMPK) activity, leading to increased CPT1 activity and enhanced fatty acid oxidation. While this might seem adaptive, chronic elevation of fatty acid oxidation can overwhelm the tricarboxylic acid cycle, leading to incomplete oxidation and accumulation of toxic intermediates [81]. These metabolic disturbances manifest clinically as impaired diastolic relaxation, the earliest functional abnormality in metabolic cardiomyopathy, progressing to reduced systolic reserve in heart failure with preserved ejection fraction phenotypes.

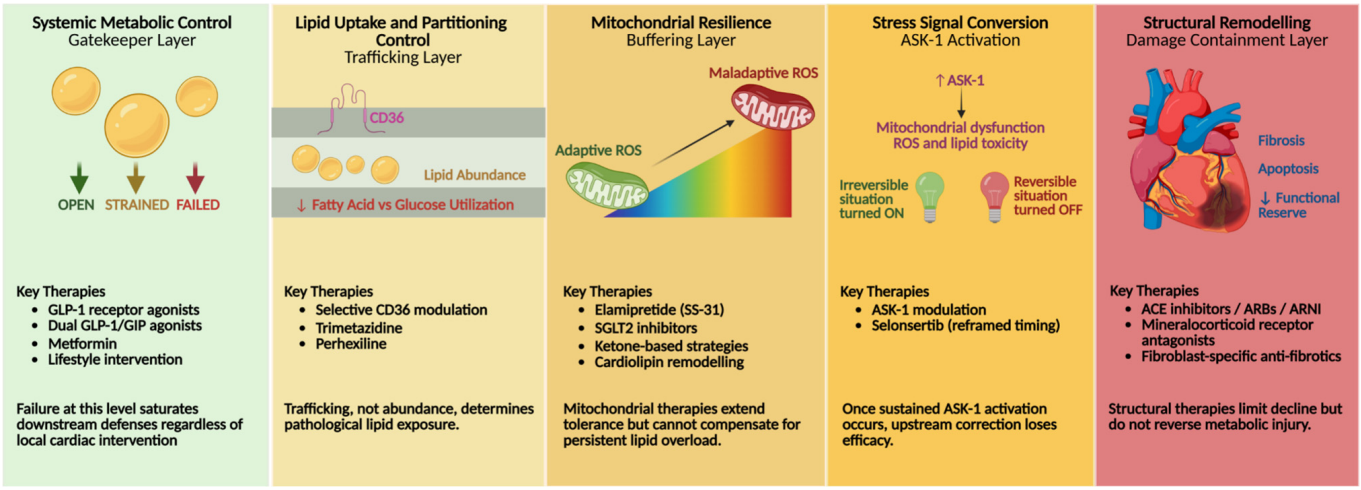


Figure 1. Hierarchical model of myocardial lipid stress progression. A hierarchical model illustrating progression from reversible metabolic dysregulation to irreversible lipid-induced cardiomyopathy. Early failure of systemic metabolic control and lipid trafficking increases myocardial lipid exposure, initially buffered by mitochondrial adaptive responses. Persistent lipid overload drives maladaptive ROS generation and activation of apoptosis signal–regulating kinase-1 (ASK-1), beyond which upstream metabolic correction loses efficacy, culminating in cardiomyocyte apoptosis, fibrosis, and loss of functional reserve. Layer 1: Systemic metabolic control regulates lipid availability; failure causes sustained lipid oversupply. Layer 2: CD36-mediated lipid uptake and partitioning; dysregulated trafficking drives pathological exposure. Layer 3: Mitochondrial resilience buffers lipid excess via cardiolipin remodeling and controlled ROS, but fails with chronic overload. Layer 4: ROS-dependent ASK-1 activation converts metabolic stress into irreversible injury signaling. Layer 5: Structural remodeling marked by cardiomyocyte loss, fibrosis, and reduced functional reserve, where therapies are palliative rather than restorative.

4.3. ASK-1 Activation and Cardiac Stress Signaling

ASK-1 is a stress-responsive MAP3K that is activated by reactive oxygen species, endoplasmic reticulum stress, and inflammatory cytokines [82]. Immune hyperactivation, such as that triggered by advanced immunotherapies, can disrupt lipid homeostasis and compromise mitochondrial function in cardiovascular tissues [83]. Under basal conditions, ASK-1 is maintained in an inactive state through association with thioredoxin. When cells experience oxidative stress, thioredoxin is oxidized, releasing ASK-1 and allowing it to oligomerize and become activated through autophosphorylation [84]. The lipid peroxidation-derived aldehydes, particularly 4-HNE, amplify ASK-1 activation through multiple mechanisms. 4-HNE directly modifies thioredoxin at critical cysteine residues, preventing its inhibitory function and maintaining ASK-1 in its active state even when cellular ROS levels transiently decrease [85]. In lipid-overloaded cardiomyocytes, the combination of elevated 4-HNE production from cardiolipin peroxidation and impaired antioxidant capacity creates a state of persistent ASK-1 activation. This represents a mechanistic transition from reversible oxidative stress to irreversible stress signaling, distinguishing early metabolic dysfunction from advanced lipotoxic cardiomyopathy. ASK-1 activation marks the transition to Layer 4 in the hierarchical model (Figure 1), representing the point where reversible metabolic stress converts to irreversible stress signaling that drives apoptosis and fibrosis even after correction of upstream lipid abnormalities.

Once activated, ASK-1 initiates two major signaling cascades, the p38 MAPK pathway and the c-Jun N-terminal kinase (JNK) pathway. Both pathways promote cardiomyocyte apoptosis, inflammation, and fibrosis. p38 MAPK activation leads to phosphorylation of transcription factors that induce expression of pro-inflammatory cytokines and pro-apoptotic proteins. JNK activation promotes mitochondrial dysfunction and activates

pro-apoptotic Bcl-2 family members [10]. These signaling events translate metabolic stress into structural remodeling, with sustained ASK-1 activation driving the transition from reversible metabolic dysfunction to irreversible tissue injury characterized by cardiomyocyte loss, replacement fibrosis, and progression toward overt systolic dysfunction.

In the context of lipid overload, ASK-1 activation is driven by mitochondrial reactive oxygen species generation and endoplasmic reticulum stress resulting from the accumulation of lipotoxic intermediates. ASK-1 Activation marks a critical transition point in the progression from metabolic abnormalities to structural heart disease. While early metabolic dysfunction and diastolic impairment may be reversible through metabolic interventions, sustained ASK-1 signaling drives irreversible pathological remodeling characterized by cardiomyocyte apoptosis, reactive fibrosis, and left ventricular hypertrophy [86]. Clinically, this manifests as the transition from asymptomatic diastolic dysfunction to symptomatic heart failure. Patients with elevated markers of ASK-1 pathway activation show accelerated progression from metabolic cardiomyopathy to clinical heart failure, reduced response to standard heart failure therapies, and increased cardiovascular mortality [82]. Studies using ASK-1 knockout mice or pharmacological ASK-1 inhibitors have demonstrated protection against diet-induced cardiac dysfunction, with reduced cardiomyocyte apoptosis, decreased inflammatory signaling, and preserved contractile function [87]. These findings identify ASK-1 as a critical mediator linking lipid excess to cardiac injury.

4.4. PPARγ Cardioprotection and CD36 Regulation

PPARγ is expressed in cardiac tissue, though at lower levels than in adipose tissue or skeletal muscle. Cardiac PPARγ regulates expression of genes involved in fatty acid metabolism, glucose utilization, and inflammatory responses [88]. Activation of PPARγ in the heart has complex effects that depend on the metabolic context and the degree of receptor activation.

Moderate PPARγ activation can be cardioprotective, enhancing lipid storage capacity and preventing accumulation of lipotoxic intermediates [89]. PPARγ also has anti-inflammatory effects, suppressing expression of cytokines and adhesion molecules. In models of cardiac hypertrophy and heart failure, PPARγ agonists reduce fibrosis, preserve systolic function, and improve survival [90].

However, excessive PPARγ activation can be detrimental. High-dose thiazolidinediones increase cardiac lipid accumulation and exacerbate heart failure in susceptible individuals. This reflects the delicate balance between beneficial lipid buffering and harmful lipid overload [91]. The optimal level of cardiac PPARγ activity likely depends on the rates of fatty acid delivery, oxidative capacity, and the presence of other metabolic stressors.

PPARγ directly regulates CD36 expression through peroxisome proliferator response elements in the CD36 promoter. This transcriptional control creates a potential feed-forward loop where PPARγ activation increases CD36 expression, enhancing fatty acid uptake, which in turn generates endogenous PPARγ ligands from fatty acid metabolism [92]. In insulin-resistant states, dysregulation of this loop contributes to excessive CD36-mediated fatty acid influx and cardiac lipotoxicity.

PPARγ also modulates ASK-1 signaling by suppressing the generation of reactive oxygen species and reducing the stimulus for ASK-1 activation. Additionally, PPARγ may directly interfere with MAP kinase signaling pathways downstream of ASK-1 [88]. This crosstalk between PPARγ and ASK-1 pathways represents a potential therapeutic target for preventing lipid-induced cardiac injury.

4.5. Cardiac Functional Phenotypes and Disease Progression

The molecular mechanisms of lipid-driven mitochondrial dysfunction, ceramide accumulation, and ASK-1 activation produce a characteristic temporal progression of cardiac phenotypes that defines therapeutic windows and guides clinical intervention. The earliest manifestation is metabolic cardiomyopathy, characterized by diastolic dysfunction with preserved systolic function. Mitochondrial energetic impairment compromises ATP-dependent diastolic relaxation, producing prolonged isovolumic relaxation time, and reduced global longitudinal strain despite normal ejection fraction [93]. Increased myocardial triglyceride content on cardiac MRI and subclinical contractile abnormalities preceded symptoms by years. This stage remains reversible through metabolic interventions targeting upstream lipid delivery and mitochondrial function. Sustained lipotoxic stress drives progression to symptomatic heart failure with preserved ejection fraction (HFpEF). Ceramide-mediated cardiomyocyte stiffening, ASK-1-driven interstitial fibrosis, and microvascular dysfunction produce exercise intolerance, dyspnea, and elevated natriuretic peptides despite maintained ejection fraction [94]. Patients demonstrate steep filling pressure increases with volume challenge and impaired coronary flow reserve. Nearly half of diabetic patients develop this phenotype, which reflects the specific vulnerability of energy-dependent relaxation to mitochondrial lipotoxicity [95]. Interventions blocking ceramide synthesis or ASK-1 activation may halt progression at this stage, though reversibility diminishes as fibrosis advances. Diabetic cardiomyopathy represents the prototypical manifestation of the skeletal muscle–heart lipid axis, combining diastolic dysfunction, concentric hypertrophy, and impaired strain in diabetic patients without coronary disease. The clinical course progresses from asymptomatic diastolic dysfunction through symptomatic HFpEF, with a subset advancing to reduced ejection fraction as cardiomyocyte loss overwhelms compensation. Once sustained ASK-1 activation, ceramide accumulation, and mitochondrial damage produce extensive cardiomyocyte death and replacement fibrosis, ejection fraction declines below 40%, and structural remodeling becomes irreversible [96]. This transition typically occurs years after metabolic abnormalities emerge.

5. The Skeletal Muscle–Heart Lipid Axis

Excess lipid accumulation within cardiomyocytes imposes sustained metabolic stress that directly affects mitochondrial function and cellular redox balance [97]. Lipid overload increases reactive oxygen species production, alters mitochondrial membrane composition, and activates redox-sensitive signaling pathways that regulate apoptosis, inflammation, and remodeling [98]. These signaling events provide a mechanistic link between myocardial metabolic remodeling and early cardiomyocyte injury. This section examines the pathways through which lipid-induced mitochondrial stress initiates intracellular signaling cascades that contribute to myocardial dysfunction. These findings support a hierarchical model in which progressive failure of systemic metabolic control, lipid trafficking and mitochondrial buffering culminates in ASK-1-dependent stress signaling and irreversible myocardial remodeling, as depicted in Figure 1.

Earlier sections established that insulin-resistant skeletal muscle releases excess lipids through dysregulated storage, uncoupled breakdown, and impaired oxidation, while the heart responds with increased lipid uptake, mitochondrial remodeling, stress pathway activation, and lost metabolic control. This section integrates these parallel changes, showing how skeletal muscle serves as the primary driver of cardiac lipid stress and how muscle communicates this stress to the heart through multiple routes, not only circulating fatty acids but also lipid-containing exosomes and bioactive myokines that propagate metabolic dysfunction across tissues.

5.1. Dysregulated Interorgan Lipid Flux in Insulin Resistance

Inter-tissue lipid flux reflects the capacity of lipid metabolism in one tissue to shape lipid handling across distant organs. Skeletal muscle, due to its large mass and high metabolic activity, is a major determinant of systemic lipid availability. When skeletal muscle lipid metabolism is dysregulated, as occurs in insulin resistance, the consequences extend beyond muscle tissue [99].

Increased skeletal muscle lipolysis, driven by dysregulated ATGL activity or impaired insulin signaling, releases fatty acids into circulation [100]. While some of these fatty acids are re-esterified within muscle or taken up by adipose tissue, a significant fraction reaches the liver and heart. The liver responds by increasing very-low-density lipoprotein (VLDL) production, further elevating circulating triglycerides. The heart, with its constitutively high CD36 expression, avidly takes up these fatty acids, leading to cardiac lipid accumulation [101].

Inter-tissue lipid flux extends beyond free fatty acids with skeletal muscle secreting lipid-containing exosomes, small vesicles that carry lipids, proteins, and nucleic acids to recipient cells. These exosomes can modulate cardiac metabolism by delivering lipid species and signaling molecules that reshape cardiomyocyte gene expression and metabolic function [102]. The composition and function of muscle-derived exosomes are altered in insulin-resistant states, potentially contributing to cardiac metabolic dysfunction. Importantly, lipid-driven myocardial stress interfaces closely with neuro-immune signaling networks, wherein metabolic overload, inflammatory activation, and autonomic imbalance converge to shape cardiomyopathy phenotypes [103].

Myokines, the peptides secreted by skeletal muscle, also participate in muscle–heart communication [104]. While most myokine research has focused on proteins such as interleukin-6, irisin, and myostatin, these factors can indirectly influence cardiac lipid metabolism by affecting systemic insulin sensitivity, adipose tissue function, and hepatic lipid production. The full repertoire of myokines and their effects on cardiac metabolism remains to be elucidated.

5.2. PPARγ-Mediated Integration of Skeletal Muscle and Cardiac Lipid Handling

PPARγ serves as a coordinating regulator of lipid metabolism across tissues. Systemic PPARγ activation with thiazolidinediones improves insulin sensitivity in skeletal muscle, reduces hepatic glucose production, and enhances adipose tissue lipid storage [105]. These effects collectively reduce circulating lipid levels and decrease lipid delivery to the heart. This coordinated transcriptional response across multiple tissues illustrates how nuclear receptor signaling integrates whole-body metabolism.

At the tissue level, PPARγ activation in skeletal muscle enhances lipid buffering capacity, reducing fatty acid efflux [106]. In the heart, PPARγ activation promotes safe lipid storage and enhances mitochondrial oxidative capacity [107]. This coordinated response across tissues illustrates how transcriptional regulation can integrate systemic metabolism.

However, tissue-specific differences in PPARγ expression and function must be considered. The same ligand may have different effects in muscle versus heart depending on receptor density, coactivator availability, and the metabolic state of the tissue. Future therapeutic strategies may benefit from tissue-selective PPARγ modulators that enhance beneficial effects while minimizing adverse consequences.

5.3. ASK-1-Dependent Stress Signaling in Insulin Resistance and Cardiac Injury

ASK-1 functions as an integrator of multiple stress signals, including oxidative stress, endoplasmic reticulum stress, and inflammatory cytokines [108]. Chronic immune activation states, including persistent viral-associated inflammatory conditions, have been

shown to exacerbate cardiovascular risk through sustained cytokine signaling and redox imbalance [109,110]. In the context of the skeletal muscle–heart lipid axis, ASK-1 activation reflects the cumulative burden of lipid overload on cellular homeostasis [5].

In skeletal muscle, ASK-1 activation contributes to insulin resistance by promoting inflammatory signaling and interfering with insulin receptor signaling [111]. This creates a feed-forward cycle where insulin resistance begets more lipid dysregulation, which activates more ASK-1 signaling. In the heart, ASK-1 activation is the final common pathway leading to cardiomyocyte death, fibrosis, and contractile dysfunction.

Targeting ASK-1 may therefore provide benefits across multiple tissues. ASK-1 inhibitors in preclinical studies have shown promise in improving both skeletal muscle insulin sensitivity and cardiac function [11]. However, ASK-1 also plays an important role in host defense and cellular stress adaptation, so complete inhibition may have unintended consequences. Identifying conditions under which ASK-1 inhibition is beneficial versus harmful will be critical for therapeutic development.

6. Translational Implications and Therapeutic Targets

The skeletal muscle–heart lipid axis offers intervention points before overt heart failure develops. Metabolic dysregulation precedes contractile dysfunction by years. Detecting these early changes requires biomarkers that reflect dysregulated muscle lipolysis, elevated circulating lipotoxic intermediates, and myocardial metabolic stress rather than structural damage [112]. Therapeutic approaches target skeletal muscle oxidative capacity, lipid droplet dynamics, PPARγ transcriptional programs, and ASK-1 stress pathways [113]. Clinical application depends on identifying patient subgroups most likely to respond and establishing the optimal window for intervention. Successful clinical translation requires identifying patient subgroups most likely to benefit and determining the optimal window for intervention. Established, guideline-based, and emerging pharmacologic approaches targeting key nodes of the myocardial lipid-driven mitochondrial stress cascade are summarized in Table 2.

Table 2. Established and emerging pharmacologic strategies targeting myocardial lipid-driven mitochondrial stress and downstream injury signaling.

A. Established and Guideline-Adjacent Therapies				
Drug/Strategy	**Clinical Status**	**Primary Cascade Node**	**Clinical Mechanism**	**Clinical Relevance**
SGLT2 inhibitors (empagliflozin, dapagliflozin) [114]	Approved (HF, T2D)	Mitochondria, ROS	Improves myocardial energetic efficiency, reduces oxidative stress	First drugs to improve HF outcomes independent of glycemia
GLP-1 receptor agonists (semaglutide, tirzepatide) [115]	Approved	Systemic lipid flux	Weight loss (Decreased circulating FFAs), improved insulin sensitivity	Reduces upstream lipid burden to the heart
Metformin [116]	Longstanding	CD36 (indirect)	Improves insulin sensitivity, limits lipid oversupply	Foundational metabolic therapy
ACE inhibitors/ARBs/ARNI [117]	Standard HF care	Fibrosis	Attenuates maladaptive remodeling	Treats downstream consequences
MRAs (finerenone, spironolactone) [118]	Approved	Fibrosis	Anti-fibrotic, anti-inflammatory	Important in later disease stages
B. Mitochondrial-Targeted and Metabolic Modulators				
Drug/Strategy	**Clinical Status**	**Primary Cascade Node**	**Clinical Mechanism**	**Clinical Relevance**
Elamipretide (SS-31) [119]	Phase II/III trials	Cardiolipin	Stabilizes cardiolipin–Electron Transport Chain interactions	Direct mitochondrial protection in cardiomyopathy
Trimetazidine [120]	Approved	FAO shift	Shifts substrate use from FA to glucose	Reduces lipid-induced mitochondrial stress
Perhexiline [121]	Restricted use	FA transport	CPT-1 inhibition limits mitochondrial FA influx	Effective but narrow safety margin
Ketone-based metabolic strategies (dietary or pharmacologic) [122]	Emerging	Mitochondria	Improves energetic efficiency (reduced ROS)	Aligns with SGLT2i mechanistic benefits
C. Recent and Emerging Strategies				
Drug/Strategy	**Clinical Status**	**Primary Cascade Node**	**Clinical Mechanism**	**Clinical Relevance**
Dual GLP-1/GIP agonists (e.g., tirzepatide) [123]	Approved	Systemic lipid flux	Greater weight loss and lipid lowering than GLP-1 alone	Strong upstream reduction in myocardial lipotoxic exposure
Selective CD36 modulation (trafficking-focused) [124]	Preclinical → early translational	CD36	Targets sarcolemma localization rather than total expression	Preserves physiological FA uptake while limiting overload
Cardiolipin remodeling enzyme targeting [125]	Preclinical	Cardiolipin	Focus on tafazzin/CL remodeling pathways	More precise mitochondrial membrane therapy
ASK-1 pathway modulation (e.g., selonsertib) [126]	Challenges in larger trials	ASK-1	Shift from chronic inhibition to early/intermittent targeting	Reframes why earlier trials underperformed
Fibroblast-specific anti-fibrotic [127]	Early clinical	Fibrosis	Cell type–specific remodeling inhibition	Avoids myocardial suppression
Exercise-mimetic metabolic modulators [128]	Early translational	Multi-node	Activate AMPK/PGC-1α–like signaling	Bridges lifestyle and pharmacology

6.1. Exercise Training and Comparative Metabolic Phenotyping of the Muscle–Heart Lipid Axis

Exercise training interventions show that changes in skeletal muscle lipid handling occur alongside measurable improvements in cardiac metabolic indices. In insulin-resistant individuals, endurance training increases skeletal muscle mitochondrial density, enhances oxidative enzyme activity, and improves the coordination between lipolysis and fatty acid oxidation [129]. These adaptations are associated with lower circulating fatty acid concentrations and reduced myocardial lipid accumulation. Intervention studies further indicate a graded relationship between training exposure and metabolic adaptation, with higher training volumes producing greater improvements in muscle oxidative capacity and parallel reductions in cardiac lipid burden [130].

Stable isotope tracer studies in humans indicate that insulin-resistant individuals exhibit elevated skeletal muscle lipolysis with incomplete oxidative disposal, leading to increased fatty acid availability in the circulation [131]. Cardiac magnetic resonance spectroscopy identifies corresponding increases in myocardial triglyceride content, which correlate with impairments in diastolic relaxation. Following structured exercise training, improvements in muscle oxidative capacity are accompanied by reductions in circulating acylcarnitines, lower myocardial lipid content, and modest improvements in indices of diastolic function [132].

Comparative metabolic phenotyping across physiological and pathological states reveals distinct patterns of lipid flux. Healthy sedentary individuals maintain balanced lipid turnover with moderate intramyocellular lipid stores and preserved cardiac function [124]. Insulin-resistant individuals without overt diabetes demonstrate increased muscle lipid content, elevated circulating fatty acids, early myocardial lipid deposition, and subclinical diastolic dysfunction detectable by advanced imaging. These abnormalities are more pronounced in type 2 diabetes, where severe mitochondrial dysfunction and systemic lipid dysregulation coincide with established metabolic cardiomyopathy. In contrast, endurance-trained athletes display high intramyocellular lipid content yet maintain efficient lipid turnover, low circulating fatty acid concentrations, preserved insulin sensitivity, and normal cardiac structure and function [133]. This phenotype indicates that absolute lipid accumulation is less informative than the balance between storage, mobilization, and oxidation in determining downstream metabolic consequences. Observations from inherited mitochondrial myopathies provide additional insight. Individuals with primary defects in skeletal muscle mitochondrial function exhibit impaired fatty acid oxidation, accumulation of circulating lipid intermediates, and an increased prevalence of cardiomyopathy, independent of obesity or diabetes status [134]. Collectively, these findings support a central role for skeletal muscle oxidative capacity in influencing systemic lipid distribution and myocardial lipid exposure without implying direct causality.

6.2. Biomarkers of Muscle–Heart Lipid Axis Dysfunction

The sequence linking skeletal muscle insulin resistance to cardiac lipotoxicity advances through distinct stages. This temporal progression presents multiple opportunities for intervention to prevent disease advancement before irreversible structural cardiac changes develop [135]. Identifying patients during these metabolically compromised yet structurally intact stages requires biomarkers that detect active lipid dysregulation in muscle, circulating lipotoxic intermediates, and early myocardial metabolic stress, rather than conventional markers that appear only after fixed structural pathology has emerged. Traditional biomarkers, such as natriuretic peptides and troponins, detect established cardiac injury but lack sensitivity for early metabolic dysfunction [136]. Novel biomarkers reflecting perturbations in the skeletal muscle–heart lipid axis may enable earlier detection and intervention.

Circulating acylcarnitines, particularly long-chain species, reflect impaired skeletal muscle mitochondrial oxidation and predict cardiovascular events [137]. Plasma ceramides and diacylglycerols correlate with insulin resistance and cardiac dysfunction. PLIN3, which is released from lipid droplets during lipolysis, can be measured in circulation and reflects skeletal muscle lipid turnover [138]. Elevated circulating 4-HNE-modified proteins potentially reflect the extent of irreversible myocardial protein modification [139]. Measurement of 4-HNE-albumin adducts offers a practical clinical assay, as albumin is abundant and readily modified by reactive aldehydes. Cardiolipin composition can be assessed in peripheral blood mononuclear cells and may reflect systemic mitochondrial stress [74]. Exosome lipid profiling could provide insights into inter-tissue lipid communication. Combining these metabolic biomarkers with traditional risk factors and imaging biomarkers, such as cardiac magnetic resonance spectroscopy for myocardial triglyceride content, may improve risk stratification [140].

6.3. Interventions Targeting Skeletal Muscle Lipid Handling and Oxidative Capacity

Improving skeletal muscle lipid handling represents an upstream intervention point for preventing cardiac lipotoxicity [16]. Exercise training is one of the most effective interventions, increasing mitochondrial content, enhancing oxidative capacity, and improving insulin sensitivity. Endurance training preferentially recruits oxidative muscle fibers and stimulates mitochondrial biogenesis through AMPK and PGC-1α activation [141]. Resistance training increases muscle mass and glycolytic capacity, creating a metabolic sink for glucose and reducing reliance on lipid oxidation [141].

Comparative studies demonstrate that trained individuals maintain metabolic flexibility despite high energy flux, whereas sedentary insulin-resistant individuals lose this adaptive capacity [142]. Athletes show enhanced capacity for lipid droplet turnover, improved matching of lipolysis to oxidation, and reduced spillover of lipotoxic intermediates into circulation. These training-induced adaptations occur across muscle fiber types, though oxidative fibers show greater capacity for metabolic remodeling. Studies examining patients with inherited mitochondrial disorders affecting skeletal muscle reveal corresponding cardiac abnormalities, further supporting the mechanistic link between muscle oxidative capacity and cardiac health [143].

Pharmacological approaches targeting skeletal muscle metabolism include AMPK activators that enhance fatty acid oxidation and mitochondrial biogenesis and PPARγ agonists that shift muscle toward oxidative metabolism and mitochondrial uncouplers, which dissipate excess reducing equivalents [144]. Each of these approaches has shown promise in preclinical studies but requires careful evaluation in humans to balance metabolic benefits against potential adverse effects.

Modulating lipid droplet dynamics through PLIN2 inhibition or DGAT1 activation may enhance lipid buffering capacity while preventing lipotoxic intermediate accumulation [145]. In addition, targeting ceramide synthesis addresses bioactive lipids. Myriocin, a serine palmitoyltransferase inhibitor, blocks de novo ceramide synthesis and prevents cardiac dysfunction, but complete depletion may be harmful [146]. CerS6-selective inhibitors reduce pathogenic C16:0-ceramide without depleting protective species, improving insulin sensitivity and cardiac function [147]. Enhancing ceramide clearance through acid ceramidase activation or adiponectin therapy reduces ceramide burden. These complement upstream lipid interventions by targeting specific toxic species. However, these interventions must be carefully titrated, as excessive lipid storage can impair insulin signaling, while excessive lipolysis increases systemic lipid burden.

6.4. Therapeutic Modulation of PPARγ Signaling

The PPARγ mechanisms described earlier in skeletal muscle and cardiac tissue as in sections before point to several therapeutic possibilities. Thiazolidinediones, the prototypical PPARγ agonists, improve insulin sensitivity and reduce cardiovascular events in diabetic patients, but their use is limited by adverse effects including weight gain, fluid retention, and heart failure exacerbation [148]. Next-generation PPARγ modulators aim to preserve insulin-sensitizing effects while minimizing cardiovascular risks [106].

Selective PPARγ modulators (SPPARγMs) are ligands that stabilize specific receptor conformations, biasing downstream signaling toward beneficial pathways [149]. These compounds show promise in preclinical studies, improving insulin sensitivity without causing weight gain or cardiac dysfunction. Clinical development of SPPARγMs is ongoing.

Tissue-selective PPARγ activation, achieved through targeting of PPARγ ligands to specific tissues or development of ligands with tissue-specific metabolism, represents another approach [150]. Enhancing PPARγ activity in skeletal muscle and adipose tissue while limiting cardiac activation might provide metabolic benefits. Complementing nuclear receptor–based strategies such as microRNA-directed therapies have emerged as powerful modulators of lipid metabolism. Dual targeting of lipid-regulatory microRNAs such as miR-33 and miR-92a has demonstrated coordinated improvements in cholesterol handling, inflammatory signaling, and vascular lipid burden, underscoring the therapeutic promise of post-transcriptional lipid control in cardiometabolic disease [71].

6.5. Modulating ASK-1 Stress Signaling to Limit Lipid-Driven Cardiac Injury

The mechanisms outlined in previous sections establish ASK-1 as both a final common pathway for cardiac lipotoxic injury and a key mediator of muscle–heart metabolic dysfunction. This dual role makes pharmacological ASK-1 inhibition a mechanistically sound therapeutic approach. Small molecule ASK-1 inhibitors have been developed and tested in preclinical models of cardiovascular disease, diabetic nephropathy, and neurodegenerative disorders [11]. These compounds prevent ASK-1 autophosphorylation and downstream signaling, reducing apoptosis and inflammation [11].

In models of diet-induced obesity and insulin resistance, ASK-1 inhibitors improve glucose tolerance, reduce hepatic steatosis, and prevent cardiac dysfunction. In models of myocardial infarction and pressure overload, ASK-1 inhibitors reduce infarct size and prevent adverse remodeling [151]. Clinical trials of ASK-1 inhibitors in diabetic kidney disease have shown safety and preliminary efficacy.

Targeting ASK-1 in metabolic cardiomyopathy offers a mechanistically grounded avenue for intervention. The challenge will be identifying patients who will benefit most from ASK-1 inhibition and determining optimal timing and duration of treatment. Biomarkers of ASK-1 pathway activation, such as phosphorylated p38 MAPK or downstream transcriptional targets, may help guide patient selection [152]. Beyond direct kinase inhibition, immunomodulatory strategies are increasingly recognized as viable approaches to mitigate lipid-driven cardiovascular injury in diabetes. Restoration of immune checkpoint signaling has been shown to attenuate diabetes-associated vascular inflammation, reduce lipid-laden plaque burden, and improve atherosclerotic outcomes, underscoring the contribution of immune–metabolic crosstalk to lipid-driven cardiovascular disease. These findings suggest that immune checkpoint pathways indirectly influence lipid handling and inflammatory stress signaling, complementing metabolic and stress-kinase–targeted interventions [71].

7. Future Directions

Critical gaps remain in translating the skeletal muscle–heart lipid axis from mechanism to bedside. Longitudinal studies integrating metabolic phenotyping, lipidomics, and

cardiac imaging will be essential to map the progression from muscle lipid dysregulation to cardiac structural damage, defining the therapeutic window before injury becomes irreversible [153]. Understanding how different muscle fiber types contribute to this process represents another priority. Oxidative fibers, enriched in endurance-trained individuals, exhibit a superior capacity for lipid handling and oxidative metabolism compared with the glycolytic fibers predominant in sedentary populations [154]. The extent to which interventions that promote oxidative fiber predominance can attenuate systemic lipid burden and confer downstream cardio protection remains an important unresolved question.

The paradox of sex differences in lipid handling deserves particular attention, given that women tolerate higher intramyocellular lipid content without developing insulin resistance and maintain cardiovascular protection through their premenopausal years through mechanisms that remain poorly defined [155]. Recent evidence implicating muscle-derived exosomes in inter-organ communication raises questions about their role in metabolic cardiomyopathy, necessitating detailed characterization of their lipid cargo and signaling properties in insulin-resistant states [156]. Finally, integrating genetic variation in lipid droplet proteins, lipases, and metabolic regulators with phenotypic outcomes will enable precision stratification of patients at risk for metabolic cardiomyopathy and guide selection of targeted interventions based on individual molecular profiles.

8. Conclusions

Chronic insulin resistance drives a persistent redistribution of lipid flux, linking skeletal muscle metabolic dysfunction to myocardial injury through coordinated inter-organ and cellular mechanisms. Impaired intramyocellular lipid droplet regulation, decoupled ATGL-mediated lipolysis and reduced mitochondrial fatty acid oxidation in skeletal muscle elevated circulating fatty acids, directly increasing myocardial lipid exposure. In cardiomyocytes, high CD36-mediated uptake, limited storage capacity, and altered cardiolipin composition destabilize mitochondrial cristae impair respiratory efficiency and increase reactive oxygen species generation, triggering ASK-1-dependent stress signaling that drives apoptosis, inflammatory gene expression, and extracellular matrix deposition. PPARγ-dependent transcriptional programs normally coordinate lipid uptake, sequestration, and oxidation across skeletal muscle and myocardium, constraining lipotoxic intermediates and stress kinase activation, disruption of this regulatory axis amplifies cardiac susceptibility to lipid-induced injury. Viewed systemically, skeletal muscle functions as a primary determinant of myocardial lipid exposure, and persistent defects in muscle lipid handling propagate fatty acid-driven mitochondrial and cellular stress in the heart. Therapeutic strategies that restore skeletal muscle lipid buffering, normalize systemic fatty acid flux, or attenuate ASK-1-mediated stress signaling may limit progression to metabolic cardiomyopathy, while integrating lipid-derived biomarkers with functional cardiac assessment could enable earlier identification of at-risk individuals. Collectively, these findings define a mechanistic pathway linking insulin resistance to myocardial remodeling and highlight interventional targets for preserving cardiac metabolic health.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/lipidology3010005/s1, Figure S1: PRISMA flow diagram of study identification and selection. Flowchart illustrating the systematic literature search and screening process. A total of 1733 records were identified from PubMed, of which 1303 records were screened after initial filtering. Following title and abstract screening, 312 reports were sought for retrieval, and 133 reports were assessed for full-text eligibility. Ninety-two reports were excluded due to irrelevant outcomes, resulting in 41 studies included in the final review.

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