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Inter-Organ Lipid Trafficking in Obesity-Induced Diabetes: From Adipose Overflow to Lipotoxic Organ Crosstalk

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ABSTRACT

Obesity-induced type 2 diabetes (T2D) is not simply a problem of "too much fat" but of where lipid ends up and how it moves between organs. Under physiological conditions, subcutaneous adipose tissue (AT) serves as a safe reservoir that buffers postprandial lipid flux, limiting exposure of non-adipose organs to toxic lipid intermediates. In obesity, however, AT becomes inflamed, fibrotic, and relatively non-expandable, leading to adipose overflow: excess fatty acids and triglyceride-rich lipoproteins spill into the circulation and are deposited as ectopic fat in liver, skeletal muscle, pancreas, heart, and kidney.Within these organs, neutral triglyceride storage in lipid droplets coexists with accumulation of bioactive lipids such as diacylglycerols (DAGs) and ceramides that interfere with insulin signaling, mitochondrial function, and cell survival, a process termed lipotoxicity. Lipid-induced stress triggers maladaptive inter-organ crosstalk mediated by adipokines, hepatokines, myokines, and extracellular vesicles, amplifying insulin resistance and β-cell failure. This review frames obesity-induced diabetes as a network disease of disordered lipid trafficking. We first outline the adipose tissue expandability and overflow hypotheses, then detail how ectopic lipid accumulation and lipotoxic intermediates drive insulin resistance and dysfunction in liver, muscle, pancreas, and heart. We next highlight emerging roles for organokines and extracellular vesicles in lipid-related signaling between tissues. Finally, we discuss therapeutic strategies that re-route lipid flux through improving adipose storage capacity, targeting ceramide and DAG synthesis, or altering lipoprotein handling and future biomarker and fluxomic approaches that may enable precision management of lipotoxic diabetes.

Keywords: lipotoxicity; ectopic fat; adipose tissue overflow; ceramides; organ crosstalk

INTRODUCTION

Energy-dense diets and physical inactivity drive weight gain, but whether obesity progresses to T2D depends critically on how excess lipid is stored and trafficked between organs. In metabolically healthy states, subcutaneous AT, particularly gluteofemoral depots, acts as a high-capacity, low-toxicity buffer for dietary fat[1]. After a meal, chylomicron-derived triglycerides (TAG) are hydrolyzed by lipoprotein lipase (LPL) on adipocyte capillaries; liberated fatty acids enter adipocytes and are re-esterified into TAG within lipid droplets. This process is coupled to adipogenesis, angiogenesis, and extracellular matrix remodeling that permit adipose expansion without major hypoxia or inflammation[1].

When adipose storage is adequate, spillover of fatty acids to non-adipose tissues is minimal. The liver receives a regulated supply of fatty acids and synthesizes VLDL to redistribute TAG; skeletal muscle primarily oxidizes fatty acids and glucose according to energy demand; pancreatic islets, the heart, and kidneys see relatively low lipid flux and retain minimal intracellular fat. Under these conditions, insulin maintains tight control of substrate partitioning by suppressing lipolysis, promoting glucose uptake, and coordinating lipid storage and oxidation across organs[2].

The problem emerges when energy intake chronically exceeds this coordinated buffering capacity. The adipose tissue expandability and overflow hypotheses propose that individuals differ in how much fat can be safely stored in AT before spillover occurs. Once subcutaneous depots reach their expansion limit, further TAG must be stored elsewhere or circulate as elevated non-esterified fatty acids (NEFA) and TAG-rich lipoproteins[3]. This concept explains why some people with high BMI remain metabolically healthy, whereas others with only modest obesity develop severe insulin resistance and T2D: the critical variable is effective adipose storage capacity, not total fat mass alone. In obesity, several processes converge to reduce this capacity. Adipocyte hypertrophy leads to local hypoxia, ECM remodeling, and recruitment of pro-inflammatory macrophages and other immune cells. Inflammatory cytokines, oxidative stress, and adipocyte senescence impair adipogenesis and promote fibrosis, which mechanically constrains further expansion. AT lipolysis becomes resistant to insulin and often heightened in visceral depots, increasing NEFA flux to the liver via the portal circulation[4–6].

As adipose buffering fails, lipids accumulate as ectopic fat within lean organs. Ectopic fat is now recognized as a powerful predictor of metabolic risk[7]. MRI and spectroscopy studies show that liver fat content, intramyocellular lipid, pancreatic fat, and epicardial/pericardial fat correlate more closely with insulin resistance and cardiometabolic events than BMI or even visceral fat volume[8]. Ectopic fat is both a marker and mediator of pathophysiology.

Importantly, triglyceride itself is relatively inert when safely sequestered in lipid droplets. The more damaging actors are bioactive lipid species such as DAGs, ceramides, acylcarnitines, and certain lysophospholipids that accumulate when lipid influx exceeds capacity for oxidation and neutral storage. These metabolites activate protein kinase C isoforms, inhibit Akt/PKB signaling, alter membrane microdomains, disrupt mitochondrial function, and trigger ER stress and apoptosis[9–11]. Collectively, these processes are termed lipotoxicity.

Lipotoxicity does not occur in isolation within each organ. Lipid-laden liver, inflamed AT, and metabolically stressed muscle secrete altered arrays of organokines, adipokines, hepatokines, myokines and release extracellular vesicles and lipoproteins with modified cargo. These circulating signals propagate stress to distant tissues, reinforcing insulin resistance and promoting β-cell dysfunction[12]. For example, pro-inflammatory adipokines from dysfunctional AT worsen hepatic insulin resistance and steatosis, while hepatokines from fatty liver impair muscle glucose uptake and adipose function. The result is a multi-organ network of lipotoxic crosstalk. Framing obesity-induced diabetes as a disorder of inter-organ lipid trafficking has several implications[12, 13]. It emphasizes adipose dysfunction and ectopic fat as upstream events, rather than viewing insulin resistance solely as a cellular defect in receptor signaling. It highlights that improving glycemia without addressing lipid flux may leave residual risk, particularly for cardiovascular and liver disease. And it suggests therapeutic strategies aimed at restoring adipose buffering capacity, reducing lipotoxic intermediates, or interrupting harmful organ-to-organ signaling.

The following sections examine this network in more detail. Section 2 discusses the biology of adipose expandability and overflow. Section 3 focuses on hepatic and skeletal muscle lipid accumulation and the generation of lipotoxic intermediates that underlie systemic insulin resistance. Section 4 extends this to pancreatic, cardiac, and renal targets where lipotoxic damage contributes to diabetes progression and complications. Section 5 explores molecular mediators of lipid-related crosstalk, including organokines and extracellular vesicles. Section 6 reviews interventions that alter lipid partitioning, from lifestyle to drugs that target ceramide pathways. Section 7 outlines biomarker and fluxomic approaches that may permit organ-specific monitoring and precision therapy in lipotoxic diabetes.

2. Adipose Tissue Expandability, Dysfunction, and Overflow

Adipose tissue is not a passive storage depot but a dynamic organ whose capacity and quality determine systemic lipid handling. The expandability hypothesis posits that each individual has a limit to how much lipid can be stored safely in AT; beyond this threshold, excess energy is diverted to lean organs[2, 3, 14, 15]. Subcutaneous AT, particularly in gluteofemoral regions, is generally more metabolically benign. It favors hyperplasia over hypertrophy, has better vascularization, and secretes higher levels of adiponectin and lower levels of pro-inflammatory cytokines. Visceral AT, especially omental depots, is more lipolytic, more inflamed, and drains directly to the portal vein, thereby exposing the liver to high NEFA flux[16–18].

In early obesity, subcutaneous AT often expands relatively healthily, maintaining insulin sensitivity and dampening NEFA release. Over time, however, sustained caloric surplus drives adipocyte hypertrophy, hypoxia, and ECM remodeling. Hypoxia-inducible pathways and mechanical stress induce collagen deposition and fibrosis, which stiffen the tissue and limit further expansion. Macrophages and other immune cells accumulate, secreting TNF-α, IL-6, and chemokines that impair insulin signaling and promote lipolysis[19, 20]. Adipogenesis becomes impaired as preadipocytes and stromal cells adopt senescent or inflammatory phenotypes. This "adipose failure" reduces the ability to recruit new small adipocytes to store incoming lipid, forcing more fat into existing hypertrophic adipocytes or away from AT entirely. Insulin resistance at the adipocyte level further increases basal and catecholamine-stimulated lipolysis, raising fasting and postprandial NEFA levels[20].

The overflow model integrates these changes. When subcutaneous depots can no longer accommodate influx, excess TAG and NEFA are diverted to visceral depots, where more active lipolysis and inflammation amplify hepatic exposure. The liver responds with increased TAG uptake, de novo lipogenesis, and VLDL secretion, often outstripping its oxidative and export capacity and leading to hepatic steatosis[21]. Importantly, adipose overflow is heterogeneous. Some individuals, particularly those with lipodystrophy or genetically limited adipogenesis, experience severe metabolic complications at relatively low BMI because their adipose storage capacity is profoundly reduced[22]. Conversely, others can expand subcutaneous depots extensively with less ectopic fat and milder insulin resistance, illustrating metabolically healthy obesity[21].

In sum, defective adipose expandability and heightened lipolysis set the stage for inter-organ lipid trafficking that underlies ectopic fat deposition. Therapeutic strategies that improve adipose function by enhancing adipogenesis, reducing fibrosis, or restoring insulin sensitivity can therefore be viewed as upstream interventions that re-route lipid flux away from vulnerable organs.

3. Ectopic Lipid Accumulation and Lipotoxic Insulin Resistance in Liver and Muscle

The liver is the primary recipient of adipose overflow via the portal circulation. In obesity, increased delivery of NEFA, together with high carbohydrate intake and hyperinsulinemia, drives hepatic TAG accumulation. De novo lipogenesis is upregulated through sterol regulatory element–binding protein 1c and carbohydrate-responsive element–binding protein, while fatty acid oxidation may be relatively suppressed. The result is metabolic-associated steatotic liver disease (MASLD), tightly linked to insulin resistance and T2D[23].

Steatosis per se is not always harmful; neutral TAG within lipid droplets can be viewed as a protective sink. The problem arises when lipid influx overwhelms the machinery that packages and stores TAG, leading to accumulation of intermediates such as DAGs and ceramides. DAGs in the plasma membrane activate specific protein kinase C isoforms (notably PKCε in hepatocytes), which phosphorylate insulin receptor substrates on inhibitory sites and blunt insulin signaling. Ceramides alter membrane microdomains, inhibit Akt activation, and promote mitochondrial dysfunction and apoptosis[23].

Similar principles apply to skeletal muscle, a major site of insulin-stimulated glucose disposal. Intramyocellular lipid content is higher in insulin-resistant individuals with obesity and T2D, but also in trained athletes who are highly insulin sensitive. The difference appears to lie in the balance between neutral TAG in dynamic lipid droplets versus bioactive intermediates and mitochondrial oxidative capacity. In insulin-resistant muscle, accumulation of specific DAG and ceramide species correlates with impaired insulin signaling and reduced glucose transport, often in the context of mitochondrial overload and incomplete fatty acid oxidation[24–26].

Multi-organ fluxomic studies using stable isotope tracers show that obesity shifts substrate handling across the liver, muscle, and heart. Hepatic gluconeogenesis and lipogenesis increase, while skeletal muscle reduces overall substrate oxidation and relies more on lipid, yet with diminished mitochondrial efficiency[27–29]. This mismatch between lipid supply and oxidative capacity fosters the accumulation of lipotoxic intermediates.

In both liver and muscle, local inflammation and ER stress intensify the impact of lipotoxic metabolites. Activation of JNK and NF-κB pathways further impairs insulin signaling and promotes production of cytokines that act in an autocrine and endocrine manner[30]. Thus, ectopic lipid accumulation emerges as both a driver and amplifier of insulin resistance. Crucially, interventions that reduce hepatic and intramyocellular lipids or specifically target ceramide synthesis can restore insulin sensitivity. Pharmacologic inhibition of serine palmitoyltransferase or dihydroceramide desaturase protects against lipid-induced hepatic insulin resistance independently of changes in total TAG, underscoring ceramides as causal mediators rather than mere correlates[30].

4. Pancreatic, Cardiac, and Renal Lipotoxicity in Diabetes Progression

Beyond liver and muscle, lipid overflow affects organs whose primary role is not fuel storage, with profound consequences for diabetes progression and complications. In the pancreas, excess NEFA and circulating TAG promote fat accumulation within and around islets. Chronic exposure of β-cells to high levels of saturated fatty acids, particularly in the presence of hyperglycemia, induces ER stress, oxidative stress, and apoptosis, a state termed glucolipotoxicity. Lipid droplets within β-cells may initially be protective, but persistent overload leads to the accumulation of ceramides and other toxic lipids that impair insulin gene expression, secretion, and cell survival[31]. Over time, β-cell mass declines and secretory capacity fails, converting compensated insulin resistance into overt T2D[32].

The heart is similarly vulnerable. Cardiac myocytes normally derive a large fraction of their ATP from fatty acid oxidation, but in obesity and diabetes, they are exposed to excess circulating fatty acids and TAG-rich lipoproteins. Myocardial triglyceride content rises, and specific DAG and ceramide species accumulate, interfering with insulin signaling, calcium handling, and mitochondrial function. This contributes to diabetic cardiomyopathy, characterized by diastolic dysfunction, reduced contractile reserve, and increased risk of heart failure, even independent of coronary artery disease[33–35].

Epicardial and pericardial fat depots add another layer, acting locally on coronary vessels and myocardium via paracrine adipokines and lipids. Ectopic cardiac fat correlates with incident T2D and cardiovascular events, supporting its role as both a marker and mediator of systemic lipotoxicity[36–38]. The kidney, while less studied in this context, also accumulates lipids in obesity and T2D, particularly within proximal tubular cells and the renal sinus. Lipotoxic injury promotes glomerulosclerosis, tubulointerstitial fibrosis, and altered sodium handling, contributing to diabetic kidney disease and hypertension[39]. Thus, adipose overflow and ectopic lipid deposition form a mechanistic bridge between obesity, diabetes, and cardiorenal complications.

Across these organs, lipotoxicity rarely acts in isolation. It interacts with hyperglycemia, advanced glycation, hemodynamic stress, and inflammation. Nevertheless, converging evidence that reduction of organ-specific fat through weight loss, bariatric surgery, or pharmacologic agents improves β-cell function, cardiac performance, and renal outcomes underscores the centrality of lipid trafficking in disease progression[39, 40].

5. Molecular Mediators of Lipotoxic Organ Crosstalk: Organokines, Lipids, and Extracellular Vesicles

Inter-organ lipid trafficking is not only about the physical flux of fatty acids and lipoproteins; it is also encoded in signaling molecules whose production is shaped by lipid status. Adipose tissue, liver, muscle, and other organs secrete a complex array of proteins, lipids, and nucleic acids packaged into lipoproteins and extracellular vesicles that together orchestrate systemic metabolism.

Adipokines are perhaps the best-characterized organokines. Adiponectin, produced mainly by healthy subcutaneous adipocytes, enhances hepatic and muscle fatty acid oxidation and improves insulin sensitivity; its levels fall in obesity and T2D. Leptin regulates appetite and energy expenditure via the hypothalamus but also modulates lipid metabolism in peripheral tissues. Pro-inflammatory adipokines such as TNF-α, IL-6, resistin, and chemerin are elevated in dysfunctional AT and promote insulin resistance, steatosis, and vascular inflammation[5, 35, 41, 42]. The fatty liver secretes its own hepatokines. Fetuin-A interferes with insulin receptor signaling and promotes adipose inflammation; FGF21 enhances fatty acid oxidation and ketogenesis but may be elevated in a state of resistance in obesity; ANGPTL proteins regulate lipoprotein lipase and thus influence TAG partitioning between AT, muscle, and heart. Other hepatokines, such as hepassocin alter gluconeogenesis and lipid handling, further linking liver fat to systemic glucose control[5].

Skeletal muscle produces myokines, including IL-6 (in its acute exercise-associated form), irisin, myostatin, and others, which modulate adipose browning, hepatic glucose production, and lipid metabolism. Obesity and physical inactivity shift this myokine profile toward a more pro-inflammatory, insulin-resistant pattern, reinforcing adverse lipid handling[8, 43]. Lipid mediators themselves act as signaling molecules. Ceramides, beyond their intracellular roles, circulate in lipoproteins and associate strongly with cardiovascular and metabolic risk. Specific ceramide subspecies predict incident T2D and cardiovascular events, making them candidate biomarkers and therapeutic targets[8, 44]. Other lipokines, such as palmitoleate and FAHFAs, may convey beneficial signals that enhance insulin sensitivity and anti-inflammatory responses.

Extracellular vesicles (EVs) released from AT, liver, and other organs add a rapidly evolving layer of complexity. EVs carry proteins, lipids, and miRNAs that reflect the metabolic state of the donor tissue. In obesity and T2D, adipose-derived EVs enriched in inflammatory mediators and specific miRNAs can induce steatosis and insulin resistance in hepatocytes, while hepatocyte-derived EVs influence adipose and muscle metabolism[2, 14, 19]. Because EV cargo is strongly shaped by intracellular lipid metabolism, they act as a vehicle of lipotoxic information between organs.

Viewed together, these organokines and EVs form a signaling network superimposed on physical lipid flux. They can either buffer the system for example, adiponectin and FGF21 promoting oxidation and storage in safer depots or propagate damage, as with fetuin-A, ceramides, and pro-inflammatory adipokines. Understanding and selectively modulating this network is an emerging frontier in treating obesity-induced diabetes.

6. Therapeutic Re-Routing of Lipid Flux in Obesity-Induced Diabetes

If obesity-induced diabetes is a disease of misdirected lipid flux, then therapy can be viewed as an attempt to redesign the traffic map: increasing safe storage, reducing toxic intermediates, and altering inter-organ signaling. Lifestyle interventions that reduce caloric excess and increase energy expenditure remain foundational. Weight loss achieved through diet and physical activity decreases liver and muscle fat, improves insulin sensitivity, and lowers circulating NEFA and TAG. Importantly, even modest weight loss can markedly reduce hepatic fat before major changes in BMI, highlighting the sensitivity of ectopic stores[29, 44].

Bariatric and metabolic surgery offer a more dramatic proof-of-principle. Procedures such as Roux-en-Y gastric bypass and sleeve gastrectomy rapidly reduce liver fat, intrapancreatic fat, and myocardial lipid content, often normalizing glycemia before substantial weight loss occurs. These changes reflect a combination of negative energy balance, altered gut hormone profiles, and shifts in bile acid and microbiota metabolism that together redirect lipid away from ectopic depots[45]. Pharmacologic therapies also reshape lipid trafficking. Thiazolidinediones, by activating PPARγ, enhance adipogenesis and expand subcutaneous AT, paradoxically increasing total fat mass while improving insulin sensitivity by pulling lipid out of the liver and muscle. This "lipid redistribution" illustrates the primacy of storage location over quantity[45].

Drugs that reduce hepatic de novo lipogenesis or VLDL production, such as ACC inhibitors or some omega-3 fatty acid formulations, lower liver fat and may improve insulin sensitivity and cardiovascular risk. SGLT2 inhibitors promote caloric loss through glycosuria and favor oxidation of fatty acids, reducing liver fat and improving heart failure outcomes. GLP-1 receptor agonists and dual/triple incretin agonists produce substantial weight loss and reductions in liver fat, with pleiotropic effects on AT inflammation and organokine profiles[46, 47]. More targeted approaches focus on lipotoxic intermediates. Experimental inhibition of ceramide synthesis via myriocin or genetic suppression of key enzymes protects against lipid-induced hepatic insulin resistance and improves systemic glucose homeostasis without necessarily reducing total TAG content[48]. Similar efforts aim at modulating DAG generation or compartmentalization. While still preclinical, these strategies underscore the causal role of specific lipid species.

Emerging interventions seek to modify organokine and EV signaling. Neutralizing fetuin-A, altering ANGPTL activity to re-distribute TAG clearance, or engineering EVs with beneficial miRNA cargo are being explored as ways to correct maladaptive organ crosstalk[48]. Ultimately, the most effective strategies likely act at multiple levels: reducing overall surplus, enhancing adipose buffering, lowering lipotoxic species, and rebalancing organokine communication. Future work will need to determine which combinations best prevent or reverse lipotoxic diabetes in specific patient subgroups.

7. Biomarkers, Fluxomics, and Future Directions in Lipid Traffic–Focused Diabetes Care

To translate the concept of inter-organ lipid trafficking into clinical practice, clinicians need tools that quantify where lipid is stored and how it moves, rather than relying solely on BMI and fasting lipids. Imaging of ectopic fat using proton magnetic resonance spectroscopy, MRI, and CT has already revealed strong associations between liver, pancreatic, cardiac, and visceral fat and metabolic risk. However, these modalities are costly and not always practical for serial monitoring[49].

Circulating biomarkers offer a complementary approach. Plasma ceramide panels stratify cardiovascular and metabolic risk and correlate with liver and visceral fat, making them promising tools for assessing lipotoxic burden and treatment response[49]. Other candidates include specific acylcarnitines, lipoprotein subspecies, adiponectin, fetuin-A, FGF21, and EV-derived miRNAs that report on organ-specific stress[42].

Fluxomics using stable isotope tracers and multi-organ modelling extends beyond static measurements to quantify real-time lipid and glucose handling across tissues. Recent multi-tissue fluxomic studies have shown how obesity shifts hepatic gluconeogenesis and lipogenesis, alters cardiac substrate preferences, and suppresses skeletal muscle oxidation[10]. Applying such platforms longitudinally in therapeutic trials could reveal whether a given intervention truly reroutes lipid flux or simply reduces pool sizes. Looking forward, several directions stand out. There is a need to map tissue-specific and species-specific lipid signatures that distinguish benign from harmful ectopic fat. Not all DAGs or ceramides are equal; chain length and saturation matter, and better characterization will refine biomarker and drug target selection. Another priority is integrating lipid traffic concepts with other axes, such as inflammation, gut microbiota, and circadian rhythms, which strongly influence lipid handling in adipose tissue and liver. Clock gene disruption and gut-derived signals can shift de novo lipogenesis and VLDL secretion, further complicating the lipid map in obesity.[50]

Clinically, a future "lipid traffic–aware" approach to diabetes might combine imaging or surrogate markers of ectopic fat, lipidomic panels for ceramides and related species, and functional assessments of hepatic and muscle insulin sensitivity. Treatment could then be tailored to predominant defects, whether impaired adipose buffering, severe hepatic lipotoxicity, or multi-organ organokine dysregulation.

CONCLUSION

In conclusion, inter-organ lipid trafficking provides a unifying framework for understanding how obesity progresses to T2D and its complications. Adipose overflow, ectopic fat, and lipotoxic organ crosstalk are not merely associations but key mechanistic drivers—and increasingly, therapeutic targets. By redirecting lipid back into safe storage, reducing toxic intermediates, and modulating the signals that organs exchange, it may be possible to change the course of obesity-induced diabetes from inevitable decline to a modifiable, even partially reversible, network disorder.

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