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Adipose Tissue Dysfunction in Obesity-Induced Type 2 Diabetes: Mechanistic Insights and Therapeutic Opportunities

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ABSTRACT

Obesity is the strongest modifiable driver of type 2 diabetes (T2D), yet the mechanistic bridge between excess adiposity and systemic dysglycemia is increasingly recognized as dysfunction of adipose tissue (AT) rather than fat mass per se. In health, subcutaneous white adipose tissue (WAT) expands via adipogenesis to safely store lipid, secretes insulin-sensitizing adipokines, and communicates with liver, muscle, pancreas, brain, and immune cells to maintain fuel homeostasis. In obesity, this plasticity is exceeded, precipitating adipocyte hypertrophy, depot-specific hypoxia, extracellular-matrix remodeling and fibrosis, mitochondrial and endoplasmic-reticulum stress, and chronic low-grade inflammation (metaflammation). These insults drive insulin resistance, catecholamine resistance, dysregulated lipolysis, and ectopic lipid deposition with lipotoxic signaling, ultimately burdening hepatic glucose production, myocellular glucose uptake, and β-cell function. Emerging insights into AT endocrine and paracrine factors classical adipokines (adiponectin, leptin), lipokines, cytokines, and extracellular vesicles highlight complex bidirectional cross-talk across organs. Converging mechanisms suggest therapeutic opportunities: weight loss through lifestyle and surgery; insulin-sensitizing agents (metformin, thiazolidinediones); incretin-based poly-agonists; SGLT2 inhibition; and investigational approaches targeting inflammation, fibrosis, mitochondrial quality control, and thermogenic/beige fat recruitment. Precision strategies that integrate depot heterogeneity, immunometabolic states, and multi-omics phenotyping may enable individualized interventions that restore AT health rather than merely shrinking fat mass. This review synthesizes current concepts linking AT dysfunction with T2D pathogenesis, surveys therapeutic avenues from lifestyle to next-generation pharmacology, and outlines outstanding questions for clinical translation.

Keywords: adipose tissue; insulin resistance; adipokines; immunometabolism; type 2 diabetes

INTRODUCTION

Type 2 diabetes (T2D) arises when chronically elevated nutrient supply meets limited metabolic flexibility across organs that coordinate glucose and lipid handling. Among risk factors, obesity is paramount, but the relationship between adiposity and dysglycemia is nuanced[1–3]. Many people with excess body mass preserve normal glycemia for years, whereas a subset develop insulin resistance and β-cell failure at comparatively modest weight gain. This heterogeneity points to adipose tissue (AT) quality its capacity to expand safely, buffer lipids, and communicate endocrine signals rather than quantity alone, as the critical determinant of metabolic risk[2, 4, 5].

AT is a distributed organ comprising white, beige, and brown depots with distinct developmental origins, innervation, vascular and lymphatic networks, and immune milieus[6–8]. In energy surplus, healthy subcutaneous white adipose tissue (WAT) expands via hyperplasia (adipogenesis), distributing triglyceride across many small, insulin-responsive adipocytes. When expandability is exceeded owing to genetic constraints, aging, sex-steroid status, or environmental factors hypertrophic adipocytes dominate[9–12]. Hypertrophy predisposes to local hypoxia, extracellular-matrix (ECM) deposition and stiffness, impaired angiogenesis, endoplasmic-reticulum (ER) stress, and mitochondrial dysfunction. The resulting cellular stress activates JNK/NF-κB signaling and the NLRP3 inflammasome, recruiting and reprogramming immune cells and shifting secretory profiles toward pro-inflammatory cytokines and chemokines[13].

These local changes propagate systemic insulin resistance (IR). Insulin's antilipolytic action weakens, elevating basal lipolysis and flux of non-esterified fatty acids (NEFA) to the liver and muscle. Ectopic lipid accumulates as diacylglycerols and ceramides, activating novel PKCs that blunt insulin signaling at IRS/PI3K/Akt nodes, impair mitochondrial oxidative capacity, and alter calcium homeostasis. In the liver, IR augments

gluconeogenesis; in skeletal muscle it diminishes GLUT4-mediated glucose uptake; in pancreatic β-cells, combined lipotoxic and glucotoxic stress compromises insulin secretion, accelerating hyperglycemia[14–16].

Adipokines and lipokines provide an additional mechanistic layer. Adiponectin declines with obesity, removing tonic activation of AMPK and PPARα pathways that promote fatty-acid oxidation and insulin sensitivity[17–19]. Conversely, leptin rises but becomes ineffective at centrally regulating appetite and peripherally modulating metabolism, a state of leptin resistance. Novel adipose-derived mediators (e.g., 12,13-diHOME, palmitoleate) and extracellular vesicle cargo (microRNAs, proteins) extend AT's communication repertoire, shaping hepatic, myocellular, and islet physiology.

Importantly, AT is not homogeneous. Visceral depots are more inflamed, fibrotic, and lipolytic than subcutaneous depots, with stronger associations to cardiometabolic risk. Brown and beige adipocytes dissipate energy through UCP1-mediated thermogenesis and lipid oxidation; reduced thermogenic capacity may exacerbate positive energy balance and dyslipidemia. Depot-specific stromal cells preadipocytes, fibroblasts, endothelial and immune subsets—coordinate remodeling, and their senescence or maladaptation underwrites fibrosis and inflammatory tone[8–10, 12].

Therapeutically, weight reduction remains foundational. Even 5–10% weight loss improves hepatic steatosis, insulin sensitivity, and glycemic control, while larger losses (via lifestyle or bariatric/metabolic surgery) can induce diabetes remission. Pharmacotherapies target complementary nodes: metformin activates AMPK; thiazolidinediones (TZDs) enhance adipogenesis and lipid partitioning via PPARγ; SGLT2 inhibitors lower glucotoxicity; incretin-based agents (GLP-1 receptor agonists and co-agonists) reduce weight and improve islet function; and emerging approaches aim to modulate inflammation, fibrosis, and thermogenesis[20]. The central thesis of this review is that restoring AT health, its expandability, endocrine balance, and immunometabolic homeostasis is both a mechanistic and practical route to preventing and treating T2D. We synthesize current knowledge, highlight therapeutic strategies, and identify gaps that future research must close to translate mechanistic insights into durable clinical benefit.

2. Adipose Tissue Dysfunction in Obesity-Induced Type 2 Diabetes: Mechanistic Insights and Therapeutic Opportunities

Adipose tissue (AT) dysfunction arises when energetic demand outpaces the organ's capacity to expand via healthy adipogenesis[21]. Hypertrophic adipocytes exhibit reduced insulin signaling, diminished glucose uptake, and impaired antilipolytic responses, leading to elevated basal lipolysis and increased delivery of non-esterified fatty acids to the liver and muscle. Local hypoxia from inadequate angiogenesis activates HIF-1α and fibrogenic programs, while ECM accumulation stiffens the niche and mechanically restrains further healthy expansion. ER stress and mitochondrial dysfunction amplify JNK/NF-κB signaling and NLRP3 inflammasome activation, recruiting pro-inflammatory macrophages and other immune cells that form crown-like structures around dying adipocytes[21, 22]. The inflammatory milieu shifts adipokine secretion toward lower adiponectin and higher leptin and resistin, further entrenching systemic insulin resistance.

Depot heterogeneity matters. Visceral adipose tissue (VAT) is more lipolytic and inflamed than subcutaneous adipose tissue (SAT), drains to the portal vein, and disproportionately exposes the liver to NEFA and cytokines that drive gluconeogenesis and steatosis. Beige/brown adipocytes, which oxidize lipid for thermogenesis, decline in number and activity with obesity and aging, reducing energy expenditure and lipid clearance[23]. Stromal populations like preadipocytes, fibro-adipogenic progenitors, endothelial and immune cells undergo senescence and phenotypic reprogramming that favor fibrosis over adipogenesis[24].

Therapeutic opportunities span lifestyle, pharmacology, devices, and surgery. Calorie reduction and physical activity decrease adipocyte size, improve insulin action, and enhance mitochondrial quality control. Metformin activates AMPK and improves hepatic and peripheral insulin sensitivity[24]. Thiazolidinediones (PPARγ agonists) promote adipogenesis, redistribute lipid from ectopic sites to SAT, and raise adiponectin, albeit with weight gain and fluid-retention risks. Incretin-based therapies such as GLP-1 receptor agonists and multi-agonists induce clinically meaningful weight loss, improve glycemia, and favorably remodel AT inflammation [25]. SGLT2 inhibitors lower glucotoxicity and improve cardiometabolic outcomes. Investigational strategies target CCR2/CCR5 chemokine axes, IL-1 family signaling, anti-fibrotic pathways, mitochondrial biogenesis and mitophagy, and recruitment/activation of beige adipocytes (e.g., cold exposure, β3-adrenergic stimulation)[25]. Ultimately, restoring AT expandability, vascularization, and endocrine balance rather than simply reducing mass offers the most coherent path to reversing the metabolic sequelae that culminate in T2D.

3. Adipokines and Endocrine Crosstalk in Glucose–Lipid Homeostasis

Adipose tissue is an endocrine organ whose secretome exerts systemic control over nutrient flux. Adiponectin is abundant in lean states, binds AdipoR1/R2 to activate AMPK and PPARα signaling, enhancing fatty-acid oxidation, improving hepatic insulin sensitivity, and exerting anti-inflammatory effects in macrophages and endothelium. Levels fall with obesity and T2D, correlating inversely with IR[9, 24, 26]. Leptin reflects energy stores and acts centrally to curb appetite and increase sympathetic tone while modulating peripheral metabolism; in common obesity, leptin resistance blunts these effects.

Beyond these classical hormones, a diverse set of adipokines and lipokines shape metabolic homeostasis. Omentin and visfatin/NAMPT influence insulin action and NAD+ biosynthesis; chemerin and retinol-binding protein 4

(RBP4) have been linked to IR and inflammation. Brown/beige adipocytes release 12,13-diHOME, which promotes fatty-acid uptake and oxidation in muscle, and batokines that facilitate thermogenic-metabolic coupling. Lipokines such as palmitoleate can signal insulin-sensitizing effects in the liver and muscle, while ceramides act as lipotoxic second messengers that impair insulin signaling and mitochondrial function[27].

Extracellular vesicles (EVs) from adipocytes and stromal cells carry microRNAs, lipids, and proteins that reprogram target tissues[28]. Obesity skews EV cargo toward pro-inflammatory and insulin-desensitizing signals that alter hepatic gluconeogenesis, myocellular insulin signaling, and endothelial function. Depot-, sex-, and age-specific patterns add further complexity[29].

Therapeutically, modulating the adipose secretome offers leverage. TZDs raise adiponectin and shift lipid partitioning. Weight loss via lifestyle, incretin therapies, or surgery normalizes multiple adipokines, dampens inflammatory cytokines (e.g., TNF-α, IL-6, IL-1β), and reduces hepatokines that drive IR[30, 31]. Experimental approaches aim to harness beneficial lipokines, boost adiponectin signaling, enhance NAD+ metabolism, or edit EV cargo. As multi-agonist peptides that combine GLP-1 with GIP and/or glucagon mature, coordinated effects on appetite, energy expenditure, and adipokine profiles may allow durable re-establishment of endocrine crosstalk that supports insulin sensitivity[32–34].

4. Cellular Stress Integration: Mitochondria, ER, Oxidative Stress, and Autophagy

Cellular stress pathways orchestrate the transition from benign adipose expansion to systemic insulin resistance. Mitochondria in hypertrophic adipocytes exhibit reduced biogenesis, fragmented networks, and impaired β-oxidation, leading to reactive oxygen species (ROS) accumulation. ROS, in turn, inhibit insulin signaling and promote inflammatory gene expression[35, 36]. In brown and beige adipocytes, diminished mitochondrial content and UCP1 function reduce thermogenesis and lipid clearance, contributing to dyslipidemia and weight gain.

ER stress is a parallel hallmark. Excess nutrient flux and lipid synthesis overload protein folding capacity, activating the unfolded protein response (UPR) via PERK, IRE1, and ATF6. While adaptive UPR initially restores proteostasis, chronic activation triggers JNK and NF-κB signaling, induces CHOP-mediated apoptosis, and promotes inflammatory cytokine production[37]. Crosstalk between the ER and mitochondria at mitochondria-associated membranes perturbs calcium homeostasis, further impairing metabolism.

Autophagy and mitophagy maintain organelle quality by recycling damaged components. Obesity suppresses these pathways in AT, allowing accumulation of dysfunctional mitochondria and lipid droplets that perpetuate stress signaling. Senescent stromal and immune cells secrete a pro-inflammatory SASP that amplifies tissue dysfunction[38, 39].

Interventions that restore organelle quality can improve systemic metabolism. Exercise enhances mitochondrial biogenesis (PGC-1α), oxidative capacity, and antioxidant defenses. Caloric restriction and some pharmacologics (metformin/AMPK activation, TZDs/PPARγ signaling) upregulate mitochondrial and lysosomal gene programs and improve adipocyte insulin action[40]. Experimental strategies include NAD+ repletion, mitochondrial-targeted antioxidants, UPR modulators, and agents that activate mitophagy or beige adipocyte differentiation. The translational challenge is to achieve durable remodeling of organelle networks and proteostasis without off-target toxicity, ideally in a depot-selective manner that maximizes metabolic benefit while minimizing adverse effects[40].

5. Immunometabolic Remodeling: Innate and Adaptive Drivers of Metaflammation

Obesity reshapes the immune landscape of adipose tissue from a regulatory, type-2-skewed milieu to a pro-inflammatory state that sustains systemic insulin resistance. In lean AT, eosinophils, type-2 innate lymphoid cells (ILC2s), and regulatory T cells (Tregs) support alternative (M2-like) macrophage phenotypes through IL-4/IL-13 signaling, promoting insulin sensitivity and tissue remodeling[11, 21]. With overnutrition, chemokines (e.g., CCL2) recruit monocytes that differentiate into inflammatory macrophages (often termed M1-like), forming crown-like structures around necrotic adipocytes. These cells secrete TNF-α, IL-6, and IL-1β, activate JNK/IKK pathways in adipocytes, and impair insulin signaling.

Neutrophils, mast cells, and dendritic cells accumulate, while T-cell populations shift toward Th1/Th17 phenotypes and B cells produce antibodies that exacerbate inflammation. The NLRP3 inflammasome senses lipotoxic and ER-stress signals, driving IL-1β/IL-18 maturation. Macrophage subsets diversify; lipid-associated macrophages (LAMs) and metabolically activated macrophages display unique transcriptional programs for lipid handling and inflammation[41]. Immune cell metabolism itself is reprogrammed—glycolysis fuels effector responses, whereas fatty-acid oxidation supports regulatory phenotypes—linking nutrient cues directly to immune tone.

Therapeutically, weight loss attenuates metaflammation across depots. Pharmacologic strategies under exploration include CCR2/CCR5 antagonism to limit monocyte recruitment, NLRP3 inhibitors, IL-1 pathway blockade, and agents that expand Tregs or ILC2s. TZDs exert anti-inflammatory effects via macrophage PPARγ, while incretin-based weight loss indirectly normalizes immune composition[41]. Microbiome-targeted approaches (prebiotics/probiotics/postbiotics) may modulate AT immunity via gut-derived metabolites. A key translational objective is precise immunophenotyping to identify which inflammatory circuits dominate in a

given individual and depot, enabling targeted, combination therapies that resolve inflammation while restoring adipogenesis and vascularization.

6. Tissue Crosstalk and Ectopic Lipotoxicity: Liver, Skeletal Muscle, and Pancreas

Adipose dysfunction propagates systemic insulin resistance through altered substrate flux and endocrine signals. Elevated NEFA delivery to the liver increases diacylglycerol (DAG) and ceramide pools that activate PKC isoforms, impair insulin receptor signaling, and stimulate gluconeogenesis while inhibiting insulin-mediated suppression of hepatic glucose output. Hepatic steatosis progresses to steatohepatitis in susceptible hosts, further amplifying inflammatory signaling and dyslipidemia[42].

In skeletal muscle, intramyocellular lipid accumulation and lipid-derived metabolites disrupt insulin-stimulated PI3K/Akt signaling and GLUT4 translocation, reducing glucose uptake. Mitochondrial oxidative capacity often lags behind lipid supply, compounding DAG/ceramide buildup. Exercise training reverses many of these defects by increasing capillarity, mitochondrial content, and insulin sensitivity independently of significant weight loss[42].

Pancreatic β-cells initially compensate for systemic IR via hyperinsulinemia. Chronic exposure to elevated NEFA and glucose triggers lipotoxic and glucotoxic stress: ER stress, oxidative damage, impaired autophagy, and dedifferentiation reduce insulin secretory capacity. Islet amyloid polypeptide aggregation and local inflammation exacerbate β-cell failure. Crosstalk via adipokines is bidirectional, adiponectin supports β-cell survival/function, whereas pro-inflammatory cytokines and certain EV cargos impair it[43].

Neuroendocrine and gut-liver axes integrate these processes. Hypothalamic inflammation and leptin resistance dysregulate appetite and sympathetic output that modulates AT lipolysis and BAT thermogenesis[44]. Gut-derived signals—short-chain fatty acids, bile acids, microbial components act through GPCRs and FXR/TGR5 pathways to influence insulin sensitivity and energy expenditure, while dysbiosis can promote endotoxemia and metaflammation. Understanding this systems-level network underscores why effective therapy often requires multi-target interventions that realign substrate partitioning, endocrine signaling, and organ-to-organ communication[44].

7. Conclusions and Future Directions: Toward Precision Metabolic Medicine

The path from obesity to T2D is paved less by sheer fat mass than by the failure of adipose tissue to expand healthfully, maintain organelle quality, and preserve an anti-inflammatory, insulin-sensitizing secretome. Mechanistically, hypertrophy, hypoxia/fibrosis, mitochondrial and ER stress, and immune remodeling converge to dysregulate lipolysis and adipokine balance, propagate ectopic lipotoxicity, and overburden β-cells. Therapeutically, durable improvements in glycemia track with restoration of AT function smaller, insulin-responsive adipocytes; better vascularization; re-established adiponectin/leptin signaling; normalized immune composition; and, where feasible, enhanced thermogenic capacity.

The near-term horizon features incretin-based poly-agonists that couple weight loss with direct metabolic benefits; continued use of metformin, TZDs, and SGLT2 inhibitors as complementary backbones; and broader access to bariatric/metabolic surgery for eligible patients. Next-generation concepts include selective PPAR modulators with improved safety, agents that resolve fibrosis and promote adipogenesis, immunotherapies that recalibrate macrophage and T-cell phenotypes, EV-based diagnostics/therapeutics, and safe activation of beige/brown fat. Digital tools (continuous glucose and activity monitoring), imaging of depot-specific composition, and multi-omics profiling can enable precision phenotyping to match therapies to dominant pathobiology in each person.

Key gaps remain: how to non-invasively measure AT health; how to reverse established fibrosis; how to target depot- and cell-type-specific pathways; and how to ensure therapies are effective and accessible across diverse populations and environments. Addressing these questions will shift diabetes care from glucose-centric management to organ-repair strategies that restore AT as a resilient buffer and conductor of whole-body metabolism, reducing the global burden of T2D.

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