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Extracellular Vesicles from Obese Adipose Tissue: Hidden Messengers in the Onset of Type 2 Diabetes

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ABSTRACT

Adipose tissue is now recognized as a complex immuno-endocrine organ that communicates with distant metabolic tissues through hormones, lipids and, increasingly appreciated, extracellular vesicles (EVs). In obesity, expanding adipose depots become inflamed, hypoxic and fibrotic, and this dysfunctional state is accompanied by a marked quantitative and qualitative shift in adipose-derived EVs released into the circulation. These vesicles, which include exosomes and microvesicles from adipocytes, adipose tissue macrophages (ATMs) and stromal cells, carry bioactive cargo such as microRNAs, proteins, lipids and mitochondrial fragments that modulate insulin signaling, inflammation and cell survival in liver, skeletal muscle, pancreatic islets and vasculature. Accumulating evidence indicates that EVs from obese adipose tissue can induce insulin resistance and glucose intolerance when transferred to lean animals or to naïve cells in vitro, and that specific miRNAs and proteins within these vesicles are sufficient to drive key features of the obese–diabetic phenotype. ATM-derived exosomal miRNAs such as miR-155 and miR-29a promote insulin resistance across liver, muscle and adipose tissue, while adipocyte-derived EVs polarize macrophages toward pro-inflammatory states, establishing a vicious cycle of adipose inflammation and systemic metabolic dysfunction.This review focuses on EVs from obese adipose tissue as "hidden messengers" in the early pathogenesis of type 2 diabetes (T2D). We outline EV biogenesis and the cellular sources of adipose EVs, describe how obesity remodels their cargo and release, and synthesize data on EV-mediated crosstalk with liver, muscle, β-cells and vascular cells. We then discuss emerging evidence that adipose EV signatures can serve as minimally invasive biomarkers of transition from obesity to T2D, and highlight therapeutic strategies that either normalize pathogenic adipose EV output or harness protective EVs from adipose-derived stem cells. Finally, we consider key challenges in translating EV biology into clinical tools, including issues of specificity, standardization and safety.

Keywords: extracellular vesicles; exosomes; adipose tissue; insulin resistance; type 2 diabetes

INTRODUCTION

Obese Adipose Tissue EVs as Early Metabolic Messengers

The global rise in obesity and type 2 diabetes has sharpened attention on how expanding adipose tissue communicates with other metabolic organs[1–3]. While adipokines and free fatty acids have long been studied as endocrine mediators, the last decade has revealed extracellular vesicles as an additional, potent communication channel. EVs are lipid bilayer–enclosed nanoscale particles released by virtually all cells, including adipocytes, immune cells and stromal cells within adipose depots. They encompass exosomes (originating from the endosomal system), microvesicles (budding from the plasma membrane) and larger apoptotic bodies, and they carry complex cargo nucleic acids, proteins, lipids and metabolites—that can be delivered to distant tissues[4, 5].

Adipose tissue is particularly prolific in EV production. Under physiological conditions, adipose-derived EVs participate in local communication between adipocytes, ATMs and stromal vascular cells, helping to coordinate adipogenesis, lipolysis, angiogenesis and immune tone. Circulating adipose EVs also reach liver, muscle, pancreas and brain, contributing to systemic energy homeostasis[6–8]. In obesity, however, this signaling landscape changes dramatically. Adipocytes enlarge and become hypoxic and stressed; ATMs accumulate and adopt pro-inflammatory, lipid-laden phenotypes; adipose stem and stromal cells shift toward senescence and fibrosis. This remodeled microenvironment alters both the quantity and quality of EVs released from adipose tissue[9, 10].

Several lines of evidence position obese adipose EVs as early drivers, not merely markers, of metabolic disease. First, EVs isolated from the adipose tissue or plasma of obese mice and humans can induce insulin resistance and inflammatory gene expression when applied to hepatocytes, myotubes or endothelial cells in vitro, even in the absence of other obese milieu factors[11]. Second, transfer of ATM-derived exosomes from obese mice into lean recipients causes glucose intolerance and reduced insulin sensitivity, while exosomes from lean ATMs can partially rescue insulin resistance in obese mice, indicating that EV cargo encodes key aspects of the metabolic phenotype [11].

Third, specific molecular constituents of obese adipose EVs have been functionally linked to insulin signaling pathways. ATM exosomes in obesity are enriched in miRNAs such as miR-155 and miR-29a that target insulin receptor substrates and other components of the insulin pathway in adipocytes, hepatocytes and myocytes, thereby propagating insulin resistance across tissues[12]. Adipocyte-derived exosomes carry proteins involved in inflammatory signaling and lipid metabolism, and can skew macrophages toward M1-like states that further impair local insulin sensitivity and increase adipose lipolysis[13–15]. Importantly, these pathogenic EV changes appear early in the course of metabolic deterioration. Experimental models show that alterations in adipose EV release and cargo can occur after relatively short periods of high-fat diet exposure, preceding overt hyperglycemia and frank T2D[12]. In humans, cross-sectional and small longitudinal studies report distinct EV signatures such as altered exosomal miRNA patterns and EV surface markers—in individuals with obesity and insulin resistance compared with lean controls, even before diabetes is diagnosed[16–18].

The idea of EVs as "hidden messengers" in obesity-induced diabetes has several conceptual implications. It suggests that adipose tissue exerts endocrine and paracrine influence not only through soluble factors but through vesicle-packaged information that can be protected from degradation, targeted via surface ligands and delivered in concentrated "packets" to specific cells. It implies that a significant fraction of inter-organ crosstalk in metabolic disease may be mediated by EV-borne miRNAs, proteins and lipids that reprogram gene expression and signaling pathways in target tissues. And it raises the possibility that selective modulation of EV biogenesis, release or cargo could attenuate systemic insulin resistance without necessarily altering all aspects of the obesogenic environment[19]. At the same time, EVs from adipose tissue are not uniformly deleterious. Vesicles released by adipose-derived stem cells (ADSCs) under lean or therapeutically modified conditions can exert anti-inflammatory and insulin-sensitizing effects, promote M2 macrophage polarization and even induce beiging of white adipose tissue, suggesting a spectrum from pathogenic to protective adipose EV phenotypes[6, 8, 20]. This duality mirrors the broader concept of adipose tissue plasticity, where the same organ can either protect against or promote metabolic disease depending on its state.

This review therefore, centers on EVs from obese adipose tissue as early, mechanistically relevant messengers in T2D pathogenesis. The next section briefly outlines EV biogenesis and the cellular sources of EVs in adipose depots. Subsequent sections examine how obesity reprograms adipose EV output, how these vesicles participate in inter-organ lipotoxic and inflammatory crosstalk, and how they might be exploited as biomarkers and therapeutic tools in obesity-related diabetes.

2. Biogenesis and Cellular Sources of Adipose Tissue Extracellular Vesicles

EVs arise through distinct but overlapping biogenetic pathways. Exosomes originate from inward budding of endosomal membranes to form intraluminal vesicles within multivesicular bodies, which then fuse with the plasma membrane to release 30–150 nm vesicles enriched in tetraspanins, ESCRT components and specific lipids. Microvesicles form by outward budding and fission of the plasma membrane, typically ranging from 100 to 1000 nm and reflecting membrane and cytosolic composition at the time of shedding. Apoptotic bodies are larger vesicles released during programmed cell death[19, 21].

Within adipose tissue, virtually all major cell types produce EVs. Mature adipocytes secrete exosomes and microvesicles that contain adipokines, lipid transport proteins, enzymes of lipid metabolism and miRNAs that regulate insulin signaling and inflammatory pathways. Adipocyte-derived EVs can act locally on neighboring adipocytes and stromal cells or enter the circulation to reach distant organs[21]. Adipose tissue macrophages represent a second important EV source. ATMs in lean adipose tissue often display alternatively activated, tissue-remodeling phenotypes, and their exosomes can support insulin sensitivity. In contrast, ATMs in obese adipose depots adopt pro-inflammatory, lipid-laden states and release exosomes enriched in specific miRNAs and cytokine-related proteins that drive insulin resistance when transferred to other tissues[21].

Adipose-derived stem cells and fibroblast-like stromal cells also secrete EVs. Under homeostatic conditions and in therapeutic preparations, ADSC-EVs carry anti-inflammatory and pro-regenerative cargo, including miRNAs that promote M2 macrophage polarization, angiogenesis and tissue repair. In obesity, stromal cell EV profiles shift toward more pro-inflammatory and fibrotic patterns, although this area is less well mapped than adipocyte and ATM EVs[22]. Endothelial cells, T cells and other immune subsets within adipose tissue likewise contribute to the local EV milieu, and their vesicles can influence vascular tone, immune recruitment and adipocyte function. The overall EV output of adipose tissue is therefore a composite of multiple cellular sources whose relative contributions change with nutritional status, depot location and disease stage[22].

Biogenesis and release of EVs are regulated by metabolic and inflammatory cues that are abundant in obesity, including lipotoxicity, hypoxia, oxidative stress and cytokine signaling. These factors alter not only EV quantity

but also cargo sorting, establishing a mechanistic link between the stressed microenvironment of obese adipose tissue and the pathogenic information exported via EVs[23].

3. Obesity-Driven Remodeling of Adipose EV Release and Cargo

Obesity increases both the number of EVs released from adipose tissue and the pathogenicity of their cargo. Studies in humans and rodents show higher circulating levels of adipose-derived EV markers in obesity and metabolic syndrome, and increased EV output from explanted obese adipose tissue compared with lean tissue ex vivo[24].

At the cargo level, obesity reprograms the miRNA, protein and lipid composition of adipose EVs. ATM-derived exosomes from obese mice are enriched in miRNAs such as miR-155 and miR-29a that target insulin receptor substrates and negative regulators of inflammatory pathways; these vesicles induce insulin resistance and inflammatory gene expression in adipocytes, hepatocytes and myocytes[24]. Adipocyte-derived EVs from obese donors carry higher levels of inflammatory mediators, components of the NF-κB pathway and molecules involved in ceramide synthesis, and can polarize macrophages toward M1-like phenotypes, deepening adipose inflammation and systemic insulin resistance[25]. Obesity also alters lipid composition within EVs. Adipose EVs become enriched in sphingolipids, including ceramides, and in oxidized lipids that can act as danger-associated molecular patterns. Such lipid cargo can directly perturb membrane microdomains and signaling in target cells, or influence inflammasome activation and mitochondrial function[25].

Depot specificity adds another layer. Visceral adipose tissue, which is more inflamed and lipolytic than subcutaneous depots, appears to produce EVs with more pro-inflammatory and insulin-resistance-promoting cargo. Differences in exosomal miRNA profiles between visceral and subcutaneous adipose tissue have been reported in individuals with obesity and T2D, potentially contributing to the stronger metabolic risk associated with visceral fat accumulation[26, 27]. Finally, temporal dynamics matter. Short-term high-fat feeding can rapidly change adipose EV profiles, while weight loss and improved insulin sensitivity reverse at least part of this remodeling. Human intervention studies indicate that substantial weight loss in individuals with obesity and T2D is accompanied by broad shifts in adipose tissue pathways and likely in EV output, although EV-focused analyses are only beginning to emerge[26].

Collectively, these findings support a model in which obesity transforms adipose EVs from relatively homeostatic signals into carriers of inflammatory, lipotoxic and insulin-desensitizing information, helping to propagate metabolic dysfunction beyond the fat pad.

4. EV-Mediated Crosstalk with Liver, Muscle and Pancreatic Islets in Early Type 2 Diabetes

Adipose-derived EVs participate in dense inter-organ communication networks that are central to T2D pathogenesis. The liver, as a primary metabolic hub and recipient of adipose-derived fatty acids, is a key EV target. EVs from obese adipose tissue can be taken up by hepatocytes, where exosomal miRNAs and proteins impair insulin signaling, promote lipogenesis and enhance inflammatory responses[28]. Experimental exposure of hepatocytes to obese adipose EVs induces features of non-alcoholic fatty liver disease and hepatic insulin resistance, including reduced Akt phosphorylation and increased expression of gluconeogenic genes[28].

Skeletal muscle, the main site of insulin-stimulated glucose disposal, is another critical EV recipient. Recent work suggests that EVs derived from adipose tissue in obesity may contribute to muscle insulin resistance by delivering miRNAs that downregulate insulin signaling components and glucose transporters, as well as by carrying lipids that disturb membrane composition. A recent Diabetes Care viewpoint highlighted EVs as plausible mediators of the skeletal muscle insulin resistance that accompanies obesity and T2D, particularly in the context of weight-loss-induced remodeling of adipose EV output[29].

Pancreatic β-cells are less studied EV targets but may be highly sensitive to adipose-derived signals. Small EVs from obese adipose tissue can reach the endocrine pancreas and modulate β-cell gene expression, survival and insulin secretory capacity. Some exosomal miRNAs implicated in hepatic and muscle insulin resistance also target β-cell transcription factors and stress pathways, raising the possibility that adipose EVs contribute to early β-cell dysfunction before overt hyperglycemia develops[29–31]. Vascular and immune cells add further complexity. Adipose EVs interact with endothelial cells to promote adhesion molecule expression, oxidative stress and endothelial dysfunction, thereby linking obesity to microvascular complications and impaired skeletal muscle perfusion. They also modulate circulating monocytes and resident macrophages in distant tissues, reinforcing a system-wide pro-inflammatory state that undermines insulin action[30].

Together, these interactions create a distributed network in which obese adipose tissue, via EVs, simultaneously impairs insulin signaling in liver and muscle, promotes steatosis and vascular dysfunction, and primes β-cells for failure. This EV-based crosstalk may help explain why improving adipose health through weight loss, pharmacotherapy or bariatric surgery often yields wide-ranging benefits across organs that exceed what would be expected from changes in adipokines or lipids alone.

5. Adipose-Derived EVs as Biomarkers of Transition from Obesity to Type 2 Diabetes

EVs have several properties that make them attractive biomarker candidates: they are stable in biofluids, carry tissue-specific cargo and surface markers, and can reflect dynamic changes in cell state. Adipose-derived EVs in plasma, identified by combinations of adipocyte or ATM markers, may therefore provide a minimally invasive window into adipose health and its contribution to metabolic risk[32]. Several studies have reported altered EV counts and cargo profiles in individuals with obesity, prediabetes and T2D. Elevated levels of EVs bearing

adipocyte markers correlate with BMI, visceral fat mass and measures of insulin resistance, while changes in exosomal miRNAs derived from adipose tissue have been associated with HOMA-IR, liver fat content and glycemic indices[32]. Some adipose-enriched exosomal miRNAs implicated in insulin signaling, such as miR-155, miR-29a and others, show promise as circulating markers of early metabolic deterioration, although specificity and robustness across populations remain to be established[18, 33].

Beyond miRNAs, proteomic and lipidomic profiling of adipose EVs is beginning to uncover signature patterns associated with metabolic health versus disease. Distinct sets of EV proteins related to inflammatory signaling, extracellular matrix remodeling and oxidative stress are enriched in obesity and T2D, while certain sphingolipid species in EVs track with cardiometabolic risk[34]. Longitudinal data are still limited but crucial. Early findings suggest that changes in adipose EV profiles may precede or accompany transitions from normoglycemia to prediabetes and from prediabetes to T2D, and that improvement in insulin sensitivity after lifestyle or surgical interventions is mirrored by partial normalization of EV cargo[34]. Systematic follow-up of EV signatures in prospective cohorts will be needed to validate their predictive value and to distinguish signals specific to adipose dysfunction from EV changes arising in other tissues.

Technical challenges remain a major barrier. Standardization of EV isolation, quantification and cargo analysis is still evolving, and distinguishing adipose-derived EVs from vesicles originating in muscle, liver or blood cells is nontrivial. Nevertheless, as single-EV and multi-omics technologies advance, adipose EV signatures may become part of composite biomarker panels that integrate imaging of ectopic fat, traditional lipids and glycemic indices to refine risk stratification for obesity-related diabetes.

6. Therapeutic Modulation of Adipose Tissue EVs: From Normalization to EV-Based Therapies

If obese adipose EVs help drive T2D pathogenesis, then reducing their pathogenicity or harnessing protective EVs becomes an appealing therapeutic concept. In practice, several levels of intervention can be envisioned, ranging from upstream modification of adipose health to direct manipulation of EV biogenesis and cargo[35, 36]. At the most fundamental level, weight loss through lifestyle change or bariatric surgery improves adipose inflammation, oxygenation and insulin sensitivity. These tissue-level changes are expected to reduce the release of pro-inflammatory, insulin-desensitizing EVs and restore a more homeostatic EV profile, although explicit EV-focused studies are only beginning to appear. The Diabetes Care report on weight-loss-induced improvements in insulin sensitivity highlighted robust remodeling of adipose pathways, prompting speculation that altered EV signaling may mediate some of these systemic benefits[37–39].

Pharmacologic agents that target adipose inflammation, lipotoxicity or fibrosis may also indirectly normalize EV output. Thiazolidinediones, GLP-1 receptor agonists and SGLT2 inhibitors all improve adipose function and systemic insulin sensitivity; whether they exert part of their effect by shifting adipose EV cargo toward less pathogenic or even beneficial profiles is an active research question[40].

More direct strategies aim at EV pathways themselves. Inhibiting ceramide synthesis or signaling, for example, reduces lipotoxicity and improves insulin sensitivity in preclinical models; this may secondarily alter EV lipid content and signaling capacity[40]. Pharmacologic modulation of specific miRNAs enriched in obese adipose EVs, using antagomirs or mimics, could theoretically blunt their deleterious effects on target tissues, although achieving tissue- and EV-specific delivery remains challenging. On the flip side, EVs from adipose-derived stem cells are being explored as therapeutic agents in their own right. ADSC-EVs have shown anti-inflammatory and insulin-sensitizing effects in models of obesity and metabolic disease, in part by delivering miRNAs that promote M2 macrophage polarization, reduce adipose inflammation and induce browning of white adipose tissue[41]. Engineering such vesicles to carry defined cargo that counteracts specific pathogenic pathways, such as miR-141-3p, to alleviate hepatic insulin resistance, represents a promising but early-stage approach[41].

Any EV-targeted therapy will need to grapple with issues of specificity, off-target effects, and long-term safety. EVs participate in many physiological processes, and global inhibition of EV release or uptake could disrupt beneficial communication. Tissue-targeted strategies, such as decorating therapeutic EVs with adipose-homing ligands or selectively modulating EV biogenesis pathways in adipocytes and ATMs, may offer more precise control but will require sophisticated delivery systems.

7. Challenges and Future Directions: Making Hidden Messengers Clinically Visible

Translating the biology of adipose-derived EVs into clinical impact for obesity-related T2D faces both conceptual and practical hurdles. Conceptually, EVs operate as part of a dense communication network that includes hormones, metabolites and cytokines; dissecting the unique contributions of EV-mediated signals to metabolic phenotypes is complex. Many EV cargo components, such as miRNAs and lipids, have intracellular roles as well, and distinguishing cause from consequence requires careful experimental design, including tissue-specific manipulation of EV biogenesis in vivo[41]. Technically, the field is still converging on standardized methods for EV isolation, characterization and quantification. Differences in centrifugation protocols, size-exclusion techniques and marker panels complicate comparisons across studies and hamper meta-analytic synthesis. Single-EV analysis and advanced imaging mass cytometry are beginning to resolve heterogeneity in EV populations, but these tools remain mostly in specialized research settings[41].

From a biomarker perspective, specificity is crucial. Circulating EVs originate from many tissues and cell types; reliably attributing an EV signature to adipose tissue requires robust combinations of surface markers, cargo patterns and perhaps isotopic or lineage-tracing approaches in experimental systems. Large, diverse cohorts

with longitudinal sampling will be needed to determine whether adipose EV signatures add predictive value beyond existing risk scores for T2D and cardiovascular complications[42]. Therapeutically, the field must balance enthusiasm for EV-based interventions with caution. Engineered EVs and ADSC-EV preparations hold promise, but issues of manufacturing scale-up, batch consistency, immunogenicity and long-term safety must be addressed. Likewise, systemic manipulation of EV release or uptake risks unintended consequences in immune surveillance, tissue repair and cancer biology[42].

Despite these challenges, the trajectory is encouraging. Rapid advances in EV biology, adipose tissue immunometabolism and omics technologies are converging to illuminate how obese adipose tissue communicates with the rest of the body. EVs occupy a central position in this communication web, integrating signals from adipocytes, ATMs and stromal cells into discrete, trackable units that can travel system-wide. In the context of obesity-induced diabetes, they appear to carry early information about emerging insulin resistance and organ stress, making them appealing candidates for both mechanistic study and clinical translation[42].

CONCLUSION

In the coming years, integrating EV metrics with imaging of ectopic fat, classical biomarkers and genetic risk scores may enable a more nuanced, "communication-aware" view of metabolic disease. For clinicians, this could translate into earlier identification of patients whose adipose tissue is broadcasting high-risk messages, and into therapies that not only lower glucose but also quieten or reprogram those messages at their source. For researchers, obese adipose EVs provide a powerful lens through which to study the transition from weight gain to overt T2D, turning previously hidden messengers into targets that can be seen, measured and ultimately modified.

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