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Extracellular vesicles in obesity: linking postprandial metabolism to metabolic dysfunction

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Obesity is a major global health burden closely linked to cardiovascular complications, particularly cardiovascular disease (CVD). Extracellular vesicles (EVs), membrane-bound particles released by most cell types, mediate intercellular communication by transporting bioactive lipids, proteins, and nucleic acids. In obesity and related metabolic disorders, shifts in EV abundance, cellular origin, and cargoes have been associated with endothelial dysfunction, insulin resistance, and thrombo-inflammation. This narrative review critically appraises how postprandial metabolism reshapes the EV profile and functionality, integrating recent omics-based and mechanistic studies while distinguishing association from causality. We also examine diet–EV interactions, including how the quantity and quality of dietary fat may reprogramme EV lipids and miRNA cargoes. Evidence for food-derived EVs is emerging, but currently supports only partial gastrointestinal resistance and context-dependent bioactivity. Throughout, we highlight key methodological constraints and emphasize pre-analytical adherence to MISEV guidelines to improve reproducibility and translational relevance. Collectively, clarifying EV dynamics in the postprandial state may advance their use as clinically meaningful biomarkers and potential targets for mitigating obesity-related metabolic dysfunction through informed dietary and lifestyle interventions.

Metabolic dysregulation in obesity: an overview

Obesity is a major health burden strongly associated with systemic complications, particularly cardiovascular disease (CVD).[1] Its multifactorial nature has driven diverse investigative approaches to disentangle molecular and physiological mechanisms underlying metabolic dysfunction. Among the most active areas, extracellular vesicles (EVs) have emerged as the key mediators of intercellular communication. Although EV classification remains operational, typically based on biogenesis, size, cellular origin, and molecular cargoes, the field commonly refers to small EVs (often enriched for exosome markers) and microvesicles. Regardless of the nomenclature, EVs are released by virtually all cell types and can carry bioactive lipids, proteins, and nucleic acids that influence distant tissues, thereby potentially contributing to obesity-related pathologies.[2]

The postprandial period offers a dynamic stress test of metabolic homeostasis. After a meal, coordinated changes in lipoprotein fluxes, endocrine signals, and inflammatory tone expose latent vulnerabilities in cardiometabolic control. Emerging evidence shows that EV profiles are highly plastic postprandially, with shifts in abundance, cellular origin, and cargoes.[3,4] These changes have been linked to endothelial activation/dysfunction, platelet–leukocyte crosstalk, and innate immune pathways, underscoring EVs as both reported and potential effectors at the intersection of metabolism and inflammation.

Mechanistically, nutrient load and lipoprotein handling (*e.g.*, chylomicrons and their remnants), lipolysis products, oxidative stress, and transient endotoxemia can modulate EV release and composition across endothelial, platelet, leukocyte, adipose, hepatic, and intestinal compartments. Alterations in EV surface markers and molecular cargoes (lipid species, miRNAs and proteins) may, in turn, affect insulin signalling, vascular reactivity, and thrombo-inflammatory pathways, providing plausible links between dietary exposure, postprandial responses, and longer-term metabolic risk.

Diet and lifestyle appear to modulate EV dynamics.[5] Human and mechanistic studies indicate that the quantity and quality of fat, overall dietary patterns, and physical activity can influence EV abundance, cellular origin, and cargoes. Evidence for food-derived EVs (FDVs) is intriguing but still preliminary; current data support partial gastrointestinal resistance and context-dependent bioactivity rather than universal systemic uptake. Accordingly, this review summarizes current knowledge on EV dynamics in the postprandial state, their involvement in obesity and related disorders, and the influence of modifiable factors, while emphasizing methodological constraints and the need for standardized

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workflows to strengthen causal inference and translational relevance. We conducted a structured literature search (January 2005–January 2025) in PubMed/MEDLINE and Web of Science using combinations of: 'extracellular vesicles' OR 'exosomes' OR 'microvesicles' AND 'postprandial' OR 'meal' OR 'dietary fat' OR 'lipemia/lipaemia' AND 'obesity' OR 'insulin resistance' OR 'endotheli' OR 'thrombo*'. We prioritized original human studies and mechanistic animal/cell models evaluating EV abundance, cellular origin, or cargoes in postprandial contexts or obesity, and included relevant reviews/guidelines (*e.g.*, MISEV). Exclusion criteria were non-English studies; nanoparticles not of biological origin; studies lacking EV characterization beyond size or a single marker; and preprints without peer review. Reference lists of eligible articles were screened for additional records. As this is a narrative review, no formal risk-of-bias or meta-analysis was performed.

Extracellular vesicles: biogenesis, cargoes, and functional relevance

EVs are membrane-enclosed carriers of diverse biomolecules that have garnered increasing attention since the discovery that they are not merely cellular waste, but active mediators of intercellular communication and tissue homeostasis.[6] EV nomenclature and classification remain operational: although terms based on size (*e.g.*, small *vs.* large EVs) or context (oncosomes and migrasomes) are used; the most common distinction refers to their biogenesis, separating small EVs of endosomal origin (often enriched for exosome markers) from microvesicles (plasma-membrane budding) and apoptotic bodies (cell death-related vesicles).[7] In practice, strict discrimination is challenging due to overlapping size ranges and marker repertories, as well as isolation-dependent biases.

Endosomal (exosome-enriched) EVs, typically ~30–150 nm, arise from inward budding of the endosomal membrane to form intraluminal vesicles within multivesicular bodies (MVBs) (Fig. 1). MVBs either fuse with lysosomes for cargo degradation or with the plasma membrane to release their intraluminal vesicles as EVs. The endosomal sorting complex required for transport (ESCRT) machinery coordinates cargo selection and membrane budding (ESCRT-0/I/II) and membrane scission (ESCRT-III), although ESCRT-independent routes have also been described, underscoring context-dependent regulation of EV biogenesis.[8] In contrast, microvesicles (~50–1000 nm) bud outward directly from the plasma membrane through phospholipid distribution and cytoskeletal remodelling (actin–myosin), while apoptotic bodies originate

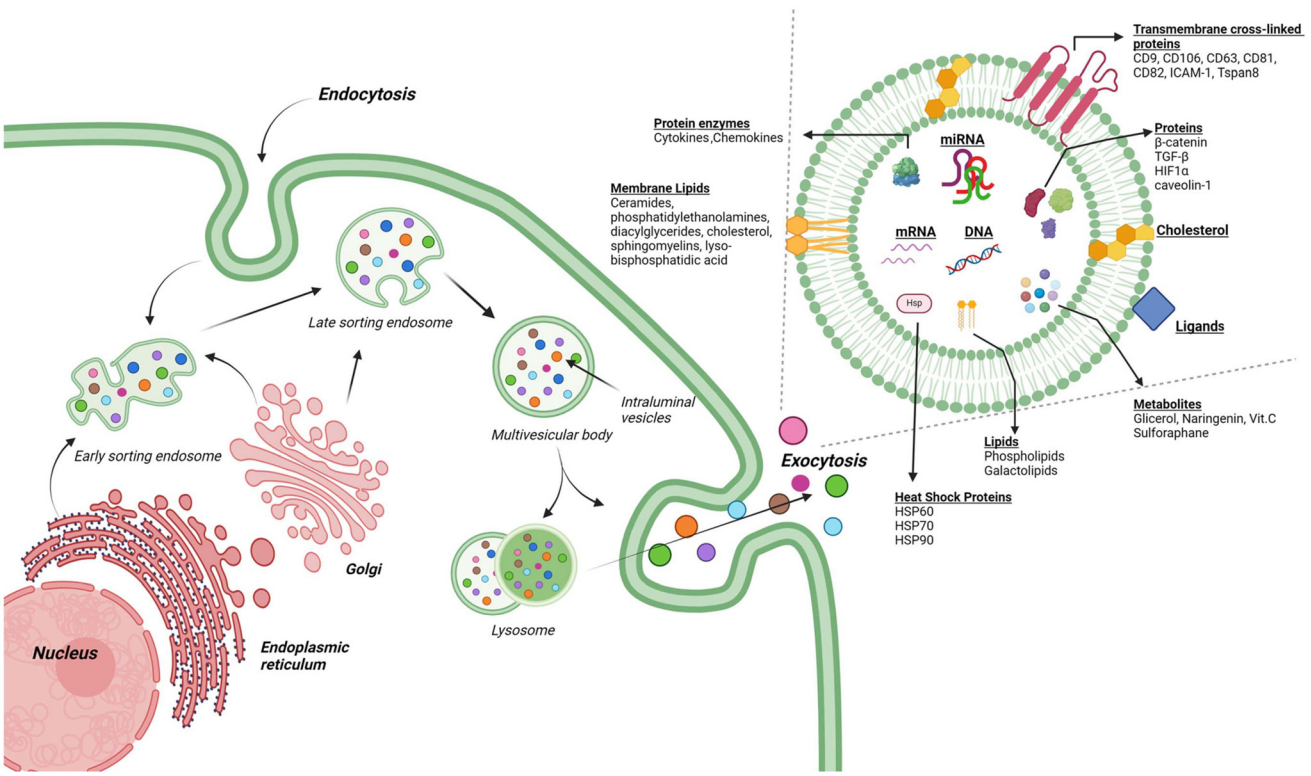

Fig. 1 Schematic representation of the biogenesis, release, and molecular composition of extracellular vesicles (EVs). EVs originate from the endosomal system through the formation of multivesicular bodies (MVBs) or *via* direct budding from the plasma membrane. The process involves endocytosis, trafficking through early and late sorting endosomes, and fusion of MVBs with the plasma membrane, leading to exocytosis and EV release. The molecular composition of EVs includes proteins (*e.g.*, β-catenin, TGF-β, HIF1α and caveolin-1), lipids (*e.g.*, phospholipids, galactolipids, cholesterol and ceramides), nucleic acids (miRNAs, mRNAs and DNAs), heat shock proteins (HSP60, HSP70 and HSP90), and metabolites (*e.g.*, glycerol, naringenin, vitamin C and sulforaphane). Transmembrane proteins (*e.g.*, CD9, CD63 and CD81) are key markers of EVs.

during programmed cell death and often contain cytoplasmic and nuclear fragments.[9]

The biological significance of EVs stems from their rich and selectable cargoes, proteins, lipids, mRNAs, miRNAs, and metabolites, and their ability to engage recipient cells *via* surface ligands/receptors, membrane fusion, and endocytosis. This enables EVs to act as both local and systemic messengers that mirror the cellular state and can modulate phenotypes in target tissues. Omics profiling (proteomics, lipidomics and transcriptomics) across EVs from multiple tissues has revealed disease-associated signatures, but also substantial methodological heterogeneity that complicates cross-study comparisons.

Protein signatures frequently reported in small EVs include tetraspanins (CD9/CD63/CD81), ESCRT-associated proteins (*e.g.*, ALIX and TSG101), scaffold/adaptor proteins, small GTPases, and other membrane/peripheral proteins (WNT).[10] Such markers have supported immunoaffinity approaches and candidate biomarker discovery, though their universality varies with cellular origin and stress context, arguing for multi-marker panels rather than single universal markers. Examples of applications to human disease include putative urinary EV protein markers for prostate cancer,[11] EV-associated proteins linked to autoimmune pathophysiology[12] and pathogen-derived proteins detected within EVs in neuroinflammatory settings.[13]

EV lipid composition is a functional determinant rather than a passive membrane scaffold. EV membranes are typically enriched in sphingolipids (*e.g.*, ceramides and sphingomyelins), cholesterol, phosphatidylethanolamines, diacylglycerols, and lysobisphosphatidic acid.[14] Disease-related remodelling of EV lipids has been reported, for instance, EVs associated with amyloid pathology showing enrichment in gangliosides/ceramides[15] and EV lipid changes linked to airway inflammation in asthma,[16] although most evidence remains correlative and sensitive to analytical workflows.

miRNAs constitute another key cargo layer. Selective sorting yields EV miRNA profiles that diverge from their parent cells, supporting regulated packaging and targeted delivery to recipient cells, where they can modulate gene expression programmes involved in differentiation, proliferation, or migration.[17] Disease-focused studies have associated EV miRNAs with tumour progression *via* repression of tumour suppressors[18] and with neurodegenerative processes and neuroinflammation.[19] As with proteins and lipids, robust interpretation benefits from integrating EV miRNAs with cellular origin markers, appropriate negative controls for contaminants, and harmonized reporting.

In summary, EVs act as both mirrors (biomarkers of cellular state) and mediators (functional effectors) of physiology and disease. Their molecular heterogeneity is biologically informative but methodologically demanding; rigorous attention to pre-analytical handling, isolation/quantification strategies, and marker panels is essential to ensure reproducibility and to translate EV insights to metabolic, neurological, oncological, and, as explored in this review, obesity-related and postprandial contexts.

Extracellular vesicles in postprandial metabolism

Postprandial lipaemia denotes the transient rise in circulating triacylglycerol (TAG) following meal ingestion, largely driven by TAG-rich lipoproteins (TRLs). Although TRLs are predominantly chylomicrons of intestinal origin, VLDLs of hepatic origin often contribute. The magnitude and duration of postprandial lipaemia depend on intestinal fat absorption, chylomicron secretion, intravascular clearance of TRLs, and VLDL metabolism/turnover.[20] This physiological process becomes pathological when TAG elevations are excessive and prolonged, a state linked to higher cardiometabolic risk. The type and amount of dietary fat, together with determinants of TRL synthesis, clearance, and re-uptake, shape the plasma lipoprotein balance.[21]

Beyond lipid excursions, the postprandial state is a period of intense metabolic–immune crosstalk. Coordinated shifts in lipoprotein fluxes, endocrine signals, and inflammatory tone can unmask vulnerabilities in cardiometabolic control. It is well established that postprandial lipaemia can induce low-grade inflammation *via* TLR/complement (C3) activation, leukocyte activation and neutrophilia, cytokine production, and oxidative stress.[22] Diets rich in saturated fatty acids (SFAs) exacerbate these responses by increasing IL-6 and TNF-α, whereas monounsaturated fatty acids (MUFAs, *e.g.*, oleic acid from olive oil)[23] and omega-3 long-chain polyunsaturated fatty acids (ω3-LCPUFAs)[24] attenuated chronic low-grade inflammation. Frequent bouts of postprandial hypertriglyceridemia contribute to the pro-inflammatory phenotype of obesity and increase CVD risk.[25]

Within this context, EVs are emerging as reporters and potential effectors of the postprandial response, although their contribution remains incompletely defined. Recent studies show postprandial shifts in EV abundance, cellular origin, and cargoes, but results for particle counts and size distributions are heterogeneous and often constrained by methodology.[5,26,27] Contributing factors include: (i) differing sampling windows (*e.g.*, 2–8 h), (ii) co-isolation with lipoproteins due to overlapping size/density, (iii) variable isolation strategies (ultracentrifugation, SEC and immunocapture), (iv) quantification platforms (NTA, flow cytometry and TRPS) with different sensitivities, and (v) normalization choices (volume, protein and cell counts). Harmonized workflows and MISEV-aligned reporting are essential to separate biological variations from technical artefacts.

Functionally, several routes connect EVs with postprandial homeostasis. EV may expose phosphatidylserine and tissue factor, determinants of procoagulant activity, linking vesicle dynamics to endothelial activation and thrombosis risk.[28] This axis remains understudied but is particularly relevant in chronically high-fat dietary patterns. Regarding lipid trafficking, Garcia *et al.*[29] reported postprandial enrichment of EVs in lipids and the CD36 fatty acid transporter, facilitating long-chain fatty acid uptake by recipient cells. These data support a role for EVs in lipid transfer from circulation to peripheral tissue; however, a key challenge is distinguishing EV-mediated transport from lipoprotein-mediated exchange, which co-occur in plasma.

At the post-transcriptional level, Mantilla-Escalante *et al.*[30] observed postprandial changes in circulating EV miRNAs, including increases in miR-206, miR-409-3p, and miR-27b-5p. The latter has been implicated in metabolic dysfunction through modulation of PPARγ and hepatic lipid metabolism.[31] While suggestive, the causal relevance of these miRNA fluctuations remains to be established and warrants mechanistic studies linking EV cargoes to metabolic endpoints in humans. Consistent with the modifiability of EV miRNAs in dietary contexts, an acute randomized crossover trial reported that a cocoa–carob blend altered exosomal miRNAs related to insulin sensitivity in type 2 diabetes, despite limited acute effects on classical glycemic/GLP-1 endpoints—highlighting EV miRNAs as sensitive readouts and the need for long-term interventions to test causality.[32]

More recently, Garza *et al.*[33] profiled the proteome and cellular origin of EVs in pre- *vs.* postprandial states. Although total EV concentrations and protein content were relatively stable, $CD324^{+}$-EVs (an epithelial intestinal marker) increased postprandially, suggesting active intestinal release in response to nutrient exposure and a potential role in gut–liver/vascular signalling. This supports the emerging view of the intestine as an endocrine organ and positions EVs as novel mediators of metabolic communication.

Collectively, current evidence supports EVs as integral components of the physiological response to nutrient intake, yet their precise contribution to postprandial homeostasis is not fully defined. Since disorders such as obesity resemble a state of sustained hyperlipidaemia, defining the phenotypic and functional properties of EVs in healthy and obese individuals should clarify mechanisms of metabolic dysregulation. Such knowledge may guide nutritional strategies to mitigate inflammatory and metabolic complications of obesity and CVD.

Extracellular vesicles in the pathophysiology of obesity

The global burden of obesity has risen sharply in recent years and continues to increase, particularly in high-income settings. According to the World Health Organisation (WHO),[34] more than one billion people worldwide were classified as obese in 2022, approximately one in eight individuals. Obesity develops when energy intake chronically exceeds expenditure, leading to excess TAG storage in adipose depots and ectopic sites. In obese individuals, lipid accumulation is accompanied by chronic low-grade inflammation, a key driver of metabolic complications including hypertension, dyslipidaemia, diabetes, CVD, and some cancers. Among the most affected organs is adipose tissue. Mammals possess white adipose tissue (WAT), primarily an energy reservoir that stores lipids and releases fatty acids for oxidation, and brown adipose tissue (BAT), which contributes to non-shivering thermogenesis and energy expenditure. Together they support metabolic homeostasis through endocrine and paracrine outputs, including hormones (*e.g.*, leptin and adiponectin), growth factors (*e.g.*, IGF-1 and VEGF), cytokines (*e.g.*, TNF-α and IL-6), and enzymes.[35] During caloric restriction, higher adiponectin is associated with improved metabolic and cardiovascular profiles. In obesity, however, the adipose tissue microenvironment is remodelled, and immune infiltration, hypoxia, and extracellular matrix changes alter secretory programmes and inter-organ crosstalk.[36] Within this disrupted dialogue, EVs have emerged as key mediators shuttling bioactive molecules between adipose depots and peripheral tissues.

A growing body of evidence implicates EVs in metabolic balance and its dysregulation in obesity (Fig. 2). Adipose tissue is a major EV source, and depot-specific differences in EV abundance and cargoes suggest that visceral and subcutaneous fat communicate differently with systemic targets. In obesity, circulating EVs enriched for pro-inflammatory factors, including IL-6, macrophage secretion inhibitory factor (MIF), and MCP-1, have been reported. MIF, for example, can promote macrophage M1 polarization *via* ERK signalling, increasing secretion of IL-1β, interferons, and chemokines.[37,38] Notably, assigning these signals to a single tissue of origin is challenging because circulating EVs are heterogeneous; rigorous attribution requires appropriate isolation, origin markers, and controls.

Among EV-associated proteins linked to adipose biology, perilipin 1 (PLIN1), a lipid droplet scaffold from the PAT family, regulates storage and lipolysis in adipocytes.[39] Under basal conditions, PLIN1 restrains ATGL and HSL activities, limiting lipolysis and downstream eicosanoid synthesis, thereby dampening macrophage recruitment and NF-κB-dependent cytokine production. In obesity, PLIN1-positive EVs are increased in circulation while adipocyte PLIN1 is reduced, a pattern associated with monocyte infiltration, cytokine release, adipose inflammation, and insulin resistance.[40] These observations support PLIN1-EVs as potential markers of adipose dysfunction; whether they act as passive indicators or active amplifiers remains to be clarified in mechanistic models. Other EV proteins, such as MMP-2, transforming growth factor beta-inducible (βig-h3), thrombospondin-1, FABP4, mimecan, and ceruloplasmin, have been reported. While FABP4 has been proposed as a marker of obesity and insulin resistance, the downstream consequences of elevated EV-associated FABP4 are not fully defined, leaving open whether these vesicles drive remodeling or primarily mirror intracellular stress.[41]

Among EV cargoes, miRNAs have attracted considerable interest because of their pleiotropic, rapid regulatory effects on adipose biology. Ferrante *et al.*[42] identified 55 differentially expressed miRNAs in exosomes from visceral adipose tissues of obese *versus* healthy controls, including downregulated miR-148b and miR-4269 and upregulated miR-23b and miR-4429, which map to TGF-β and Wnt/β-catenin pathways influencing growth, differentiation, and immune responses. Although compelling, these associations remain correlative; causal contribution to systemic insulin resistance or adipose inflammation requires functional validation.

Further insights come from work showing that adipocyte-derived EVs from obese individuals overexpress miR-34, which inhibits polarization toward the anti-inflammatory M2 pheno-

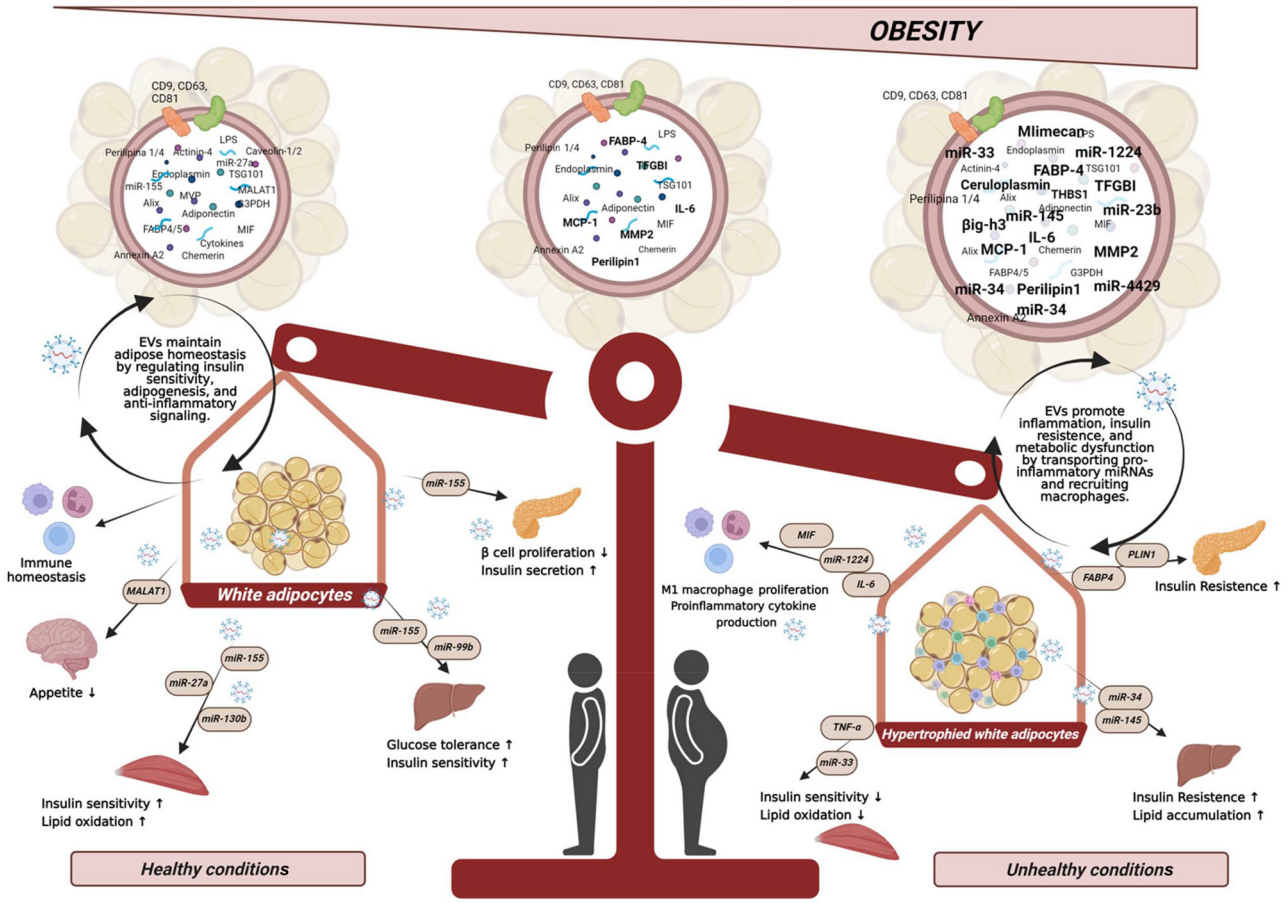

Fig. 2 Adipose tissue-derived extracellular vesicle (EV) cargoes and their alteration in the course of obesity. Under healthy conditions, EVs derived from white adipocytes contribute to adipose tissue homeostasis by regulating insulin sensitivity, adipogenesis, and anti-inflammatory signaling. These EVs transport bioactive molecules, including miRNAs (*e.g.*, miR-155, miR-27a and miR-130b), proteins (*e.g.*, adiponectin and MIF), and lipids, which support immune homeostasis, improve glucose tolerance, enhance insulin sensitivity, and promote lipid oxidation. In obesity, hypertrophied white adipocytes release EVs enriched in pro-inflammatory miRNAs (*e.g.*, miR-34, miR-33, miR-145 and miR-1224), proteins (*e.g.*, FABP4, IL-6 and MCP-1), and other factors that drive macrophage recruitment and polarization towards the pro-inflammatory M1 phenotype. These alterations promote chronic inflammation, insulin resistance, and metabolic dysfunction, leading to systemic insulin resistance, increased lipid accumulation, and decreased lipid oxidation.

type, thereby sustaining inflammation and metabolic dysregulation.[43] Likewise, miR-1224 in adipocyte-derived exosomes targets MSI2 and inhibits Wnt/β-catenin, impairing M2 polarization.[44] Conversely, miR-690 levels in M2 macrophage-derived exosomes are reduced in obesity, contributing to impaired NAD^+ biosynthesis and insulin resistance.[45] Together, these studies support bidirectional EV-mediated communication between adipocytes and immune cells; however, the temporal sequence, depot specificity, and *in vivo* effect sizes remain to be defined.

Beyond adipose-derived vesicles, endothelial- and platelet-derived EVs are altered in obesity and may contribute to cardiovascular risk. Elevated endothelial EVs enriched in adhesion molecules (VCAM-1 and ICAM-1) are reported in individuals with impaired glucose metabolism, consistent with vascular inflammation.[46] Platelet-EVs, increased in obesity, carry cytokines (*e.g.*, IL-1β, TNF-α and CCL-2), adhesion molecules (*e.g.*, ICAM-1), lipid mediators, and damage-associated molecular patterns, thereby amplifying inflammation, leukocyte recruitment, and thrombogenesis.[47,48] These vesicles also transport miR-155, a pro-inflammatory regulator implicated in adipose–muscle and vascular crosstalk.[49]

Macrophage-derived EVs further shape metabolic homeostasis. Adipocyte EVs promote macrophage accrual and M1 polarization within adipose tissue, while macrophage-EVs signal to distant organs. Ying *et al.*[50] showed that obesity-associated pro-inflammatory exosomes enriched in miR-155 suppress PPARγ signalling, impair B-cell function, reduce insulin secretion, and promote diabetes development (Table 1). Systemic characterization of macrophage-derived EV content and function in adipose tissue remains a priority.[51]

In sum, EVs are not merely bystanders but active participants in the disrupted communication networks of obesity. Their ability to transfer lipids, proteins, and genetic material across tissues places them at the interface of metabolic and immune regulation. However, progress is currently limited by

Table 1 Evidence for the contribution of the molecular content of EVs in the pathophysiology of obesity

EV component	EV origin	Source of EVs	Function in obesity	Ref.
IL-6, MIF and MCP-1	Circulating exosomes	Human plasma	Promote M1 macrophage polarization *via* ERK activation and inhibit neutrophil apoptosis, exacerbating inflammation	37 and 38
PLIN1	Adipocyte-derived exosomes	Animals (diet-induced obese mice)	Elevated in circulation; associated with altered lipid metabolism, increased adipose tissue inflammation, and insulin resistance	40
MMP-2, βig-h3, thrombospondin-1, FABP4, mimecan, ceruloplasmin, TGFBI, CD14, CAVN1 and AHNAK	Visceral adipose tissue-derived exosomes	Humans (adipose tissue from obese subjects)	Enriched in VAT-EVs from obese individuals; associated with adipose tissue inflammation, insulin resistance, and metabolic dysfunction. TGFBI-EVs were linked to T2D progression, while mimecan-EVs correlated with visceral adiposity	41
miR-148b, miR-4269, miR-23b and miR-4429	Visceral adipose tissue-derived exosomes	Humans (obese patients)	Dysregulated in obesity; modulate TGF-β and Wnt/β-catenin signaling, impacting adipogenesis, inflammation, and metabolic homeostasis	42
miR-34a	Adipocyte-derived exosomes	Animals (diet-induced obese mice)	Inhibits M2 macrophage polarization by targeting Krüppel-like factor 4 (KLF4), leading to sustained adipose tissue inflammation and metabolic dysfunction	43
miR-1224	Adipocyte-derived exosomes	Animals (HFD-induced obese mice)	Inhibits M2 macrophage polarization *via* MSI2-mediated Wnt/β-catenin signaling, promoting obesity-induced adipose tissue inflammation	44
miR-690	M2 macrophage-derived exosomes	Animals (HFD and ApoE−/− mice)	Reduces exosomal levels of miR-690, impairing NAD+ biosynthesis and contributing to insulin resistance in obesity	45
Microparticles enriched in VCAM-1 and ICAM-1	Endothelial-derived EVs	Humans (plasma, prediabetic and T2D subjects)	Elevated in obesity; these EVs are associated with endothelial inflammation and vascular dysfunction, contributing to increased cardiovascular risk in obese individuals	46
IL-1β, TNF-α, CCL-2, ICAM-1 and lipid mediators	Platelet-derived and endothelial-derived EVs	*In vitro* (human endothelial cells stimulated with TNF-α)	Transport inflammatory cytokines and lipid mediators, promoting thrombosis and leukocyte recruitment, and amplifying the inflammatory environment, contributing to obesity-related cardiovascular complications	47 and 48
miR-155	Visceral adipocyte-derived exosomes	Animals (HFD-induced obese mice; adipose–muscle co-culture and AAV model)	Impairs skeletal muscle homeostasis by inhibiting myogenesis directly through exosomal miR-155 transfer and indirectly *via* macrophage-mediated inflammation	49

heterogeneous study designs, small cohorts, and variable isolation/characterization methods. Future work should integrate standardized EV workflows with multi-omics and clinically anchored endpoints to determine whether EV modulation is predominantly a consequence or a driver of obesity, and whether nutritional interventions or specific dietary components can meaningfully recalibrate EV-mediated signaling to reverse metabolic disease.

Dietary modulation of extracellular vesicles and the role of food-derived vesicles

Given the positioning of EVs at the crossroads of metabolism and inflammation, diet emerges as a plausible lever to modulate EV abundance, cellular origin, and cargoes. Conceptually, EV-associated molecules linked to obesity (*e.g.*, specific lipids, proteins and miRNAs) could serve as biomarkers of dietary exposure and metabolic status, and, in the longer term, as modifiable targets for nutrition-based strategies. However, direct evidence in humans remains limited, and findings are often constrained by heterogeneous protocols and small samples. Rigorous, MISEV-aligned designs are needed before EVs can be incorporated into routine nutritional phenotyping.

Dietary patterns as modulators of EV profiles

Lifestyle interventions reveal the plasticity of EVs, although most studies emphasize phenotypic counts/markers rather than molecular cargoes. High-fat diets have long been linked to increased circulating EVs: for example, Heinrich *et al.*[52] reported higher plasma EVs in obese rats fed a high-fat diet, alongside enhanced endothelial VCAM-1 expression induced by these vesicles, consistent with a more pro-atherogenic milieu. In humans, recent evidence suggests that weight loss, achieved *via* diet, combined diet-plus-exercise, or bariatric surgery, can reduce circulating leukocyte- and platelet-derived

EVs – vesicle classes implicated in thrombosis and elevated cardiovascular risk.[53,54] Thrush *et al.*[55] showed that plasma exosomes from weight-loss responders (*vs.* weight-loss resistant individuals) enhanced fatty acid metabolism and increased resting, drug stimulation, and maximal oxygen consumption in cultured myotubes. These observations indicate that metabolic benefits after dietary intervention likely involve qualitative remodeling of intercellular communication *via* EVs, not merely weight reduction *per se*.

The impact of diet on EV cargoes is less well understood but is emerging. Both the amount and composition of dietary lipids appear to shape EV content and, potentially, function. For instance, perilipin A levels increase in plasma EVs from mice on high-fat diets.[56] Palmitate-rich diets can promote exosome release from muscle cells with higher lipid content, potentially mediating palmitate's adverse effects on neighbouring tissues and contributing to insulin resistance and type 2 diabetes.[57] In adipocytes, exposure to oleate *vs.* palmitate alters the protein cargoes of adipose-derived EVs, reinforcing the idea that dietary lipids reprogramme EV composition and signalling.[58] Whether such lipid-driven cargo shifts are adaptive responses or early markers of lipotoxicity remains unresolved and will be critical for interpreting EVs as biomarkers of lipid quality.

Building on these findings, Kumar *et al.*[59] observed that intestinal epithelial-derived exosomes undergo phospholipid remodelling (phosphatidylethanolamine/phosphatidylcholine balance), promoting insulin resistance through AhR activation in hepatocytes, in high-fat diet-fed mice. Lysophosphatidylcholine increases in plasma with high-fat diets, and Hirsova *et al.*[60] found that lysophosphatidylcholine-treated hepatocytes released larger EVs enriched in integrin β1, fostering inflammation. Given lysophosphatidylcholine's role in macrophage recruitment,[61] dietary patterns that elevate lysophosphatidylcholine may contribute to chronic low-grade inflammation *via* hepatocyte EV remodelling, suggesting that lowering lysophosphatidylcholine could be a nutritional avenue to attenuate EV-mediated inflammation. High-fat diets are also linked to MAFLD. Yan *et al.*[62] reported that such diets increase plasma exosomes enriched in CD36, associated with hepatic lipid accumulation and inflammation. Cholesterol loading likewise alters EV profiles: Huh7 hepatocytes exposed to oxLDL release exosomes enriched in miR-122-5p, which promote macrophage M1 polarization.[63] Collectively, these mechanistic studies support vesicle-mediated lipid trafficking as a pathogenic link between dietary fat excess, hepatic steatosis, and systemic inflammation.

Beyond lipid cargoes, nutrition influences EV miRNA profiles. Parrizas *et al.*[64] observed that a hypocaloric diet reduced miR-192 and miR-193 in obese individuals, miRNAs previously associated with liver dysfunction[65] and immune dysregulation,[66] respectively, suggesting alignment between EV miRNA shifts and improved tissue function. Manning *et al.*[67] reported dysregulated EV miRNAs in obese women (implicated in cardiometabolic processes, cardiomyocyte survival, and β-cell maintenance), with normalization after weight loss. Furthermore, Mantilla-Escalante's group[68] found that one-year adherence to a Mediterranean diet rich in olive oil and nuts reduced miR-107 (linked to hepatic lipid accumulation/FLD), while miR-22-3p, a proposed therapeutic target for obesity/insulin resistance, also decreased.[69] These clinical observations support the modifiability of EV miRNAs with realistic dietary patterns, though stability, tissue specificity, and functional causality remain open questions.

Food-derived extracellular vesicles and their therapeutic potential

While the preceding sections focused on how diet and lifestyle modulate endogenous EVs, growing interest now centers on FDVs as putative bioactive components. Diverse plant- and animal-derived foods contain vesicle-like particles that can influence cellular processes in experimental systems. Although early interpretations were uncertain, current evidence indicates and supports partial gastrointestinal resistance of only a minority fraction of FDVs; survival and uptake appear highly context-dependent (source, isolation protocol, structural features, and food matrix).[70] The vesicular phospholipid bilayer may confer limited protection, enabling some particles to be internalized by intestinal epithelial cells and to act locally in the gut; systemic actions have been reported in preclinical models but remain incompletely established in humans. Across studies, findings depend strongly on EV origin and methodology, underscoring the need for standardized isolation/characterization and label-based tracer approaches before inferring bioavailability or tissue delivery.

FDVs from blueberries and citrus (*e.g.*, lemon) have been reported to contain vitamin C and specific miRNAs that mitigate oxidative stress, reducing reactive oxygen species and improving cell viability in *in vitro*/animal models,[71] with potential relevance to obesity-related complications such as diabetes.[72] *Aloe vera* peel-derived vesicles have shown antioxidant activity linked to Nrf2 pathway activation.[73] Consistent with this, Zhao *et al.*[74] found that blueberry-derived vesicles attenuated oxidative stress, promoted nuclear translocation of Nrf2, and improved insulin resistance and liver dysfunction in a high-fat diet model, an important step toward causal mechanisms connecting dietary vesicle intake to metabolic outcomes. Translation to humans, however, remains to be demonstrated. Several plant FDVs exhibited immunomodulatory properties. Ginger-derived vesicles can deliver cargoes to macrophages, suppressing NLRP3 inflammasome activation[13] and increasing anti-inflammatory mediators such as HO-1 and IL-10.[75] Similar effects have been described for FDVs from grapefruit[76] and garlic.[13] Together, these observations support the concept that FDVs may tune host immune tone and redox balance, although the specific causal molecules (lipids, proteins and small RNAs) and their *in vivo* exposure–response relationships require clarification.

Among animal-derived foods, milk is the most extensively studied due to its abundance of vesicles. Omics profiling of milk-derived exosomes has identified miRNAs associated with diabetic complications,[77] motivating investigation into their role in human metabolic alterations and obesity. Owing to putative stability and bioavailability, milk-derived exosomes are

being explored as natural drug-delivery carriers for metabolic indications. Recent work shows efficient encapsulation and transport of bioactives, reinforcing their potential as nanocarriers for therapeutic and functional applications.[78] These findings highlight the dual significance of FDVs, as intrinsic dietary bioactives and as innovative delivery vehicles in nutritional pharmacology. In summary, FDVs are increasingly recognized as bioactive dietary components with therapeutic potential, but clinical translation will require standardization, rigorous validation, and a deeper mechanistic understanding of exposure, bioavailability, and target engagement in humans.

Concluding remarks and future perspectives

This review highlights the intricate links between EVs, obesity, and metabolic disorders, with a specific focus on the postprandial state and dietary influence. EVs are not passive carriers but active mediators of intercellular communication that intersect metabolic and immune regulation. By shaping pathways related to inflammation, lipid handling, and insulin action, EVs are emerging as both biomarkers and candidate targets for metabolic risk modification.

The postprandial period provides a sensitive stress test of cardiometabolic control. Meal composition, especially the amount and quality of dietary fat, can remodel EV abundance, cellular origin, and cargoes, with implications for endothelial activation, thrombo-inflammation, and tissue fuel partitioning. In parallel, FDVs constitute a promising but still nascent area: current evidence supports partial, context-dependent gastrointestinal resistance of a minority fraction, with plausible local gut effects and only provisional support for systemic actions in humans.

Future research should prioritize several key areas. First, mechanistic resolution of inter-organ EV signalling in obesity. Deploy causal frameworks (randomized dietary interventions and mediation/perturbation analyses) that link defined EV changes to clinically anchored endpoints (insulin sensitivity, vascular function and thrombotic markers). Second, reduce technical variability *via* MISEV-aligned pre-analytical handling, harmonized sampling windows in postprandial studies, and transparent reporting of isolation/quantification methods (*e.g.*, differential ultracentrifugation *vs.* SEC/gradients *vs.* immunocapture).[79] Include orthogonal particle and cargo quantification and normalization strategies. Mitigate lipoprotein co-isolation using apoB depletion and density/size separation. Third, integrated multi-omics and cell-of-origin mapping. Combine lipidomics, proteomics, and small-RNA profiling with robust origin markers and negative controls for contaminants to move from association to mechanism. Fourth, test whether dietary patterns (*e.g.*, fat quality, energy balance and timing) can recalibrate EV profiles in ways that predict or mediate health improvements and assess durability after weight loss or maintenance. Fifth, in humans, prioritize label-based tracer studies (stable isotopes/orthogonal labels), dose–response, and rigorous negative controls to determine true absorption, tissue delivery, and target engagement before inferring systemic effects or clinical utility.

Advances in high-throughput EV characterization coupled with computational modelling and machine learning will accelerate pattern discovery and hypothesis generation. Yet meaningful translation requires that analytical sophistication be matched by methodological discipline. By uniting standardized workflows, mechanistic insights, and clinical endpoints, the field will be better positioned to convert EV biology into actionable nutritional and therapeutic strategies for improving metabolic health.

Author contributions

Conceptualization, S. M.-d. l. P.; investigation, E. M.-P.; resources, S.M.-d. l. P.; writing – original draft preparation, E. M.-P.; writing – review and editing, S. M.-d. l. P. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

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