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# Extracellular Vesicles:

## key modulators in the development of diabetes

### EXTRACELLULAR VESICLES IN DIABETES

**Extracellular vesicles (EVs)** are small membrane-bound nano-spheres released by all the body's cells and can therefore be found in any biological fluid such as blood, urine, tears, and breast milk, among others. Depending on their origin and size, up to 3 different types of vesicles can be identified: **microvesicles** (100 nm–1 µm), derived from the »

» outward budding of the cell membrane; **exosomes** (30–100 nm), originating from within the cell and secreted via exocytosis; and **larger vesicles** (50–5000 nm), also called apoptotic bodies, released by cells after cell death or apoptosis. Initially, these vesicles were thought to function primarily in the disposal of cellular waste, but they were later rediscovered as a new **mechanism of intercellular communication**, alternative to classical pathways involving secreted soluble molecules. This new mode of communication is largely due to their composition: not only do they carry membrane proteins that can direct them to a specific target cell or tissue, but they also transport various bioactive molecules inside, such as proteins, DNA, and different types of RNA. This **molecular cargo** is precisely what makes them so interesting because, on the one hand, they represent the physiological or pathological state of the originating cell, making them valuable reservoirs of biomarkers; and on the other hand, they play a functional role by interacting with target cells or tissues. This interaction can trigger intracellular signaling in the target cell or even alter gene expression through inhibitory RNA molecules they carry, such as microRNAs (miRNAs). Specifically, in diabetes, various miRNAs traveling within EVs regulate key signaling pathways to preserve insulin sensitivity, thus playing a role in the development of insulin resistance. Therefore, EVs act as true cellular **Trojan horses** capable of influencing the function of cells and tissues not only locally but also at a distance, since they can travel through the bloodstream, even reaching the brain.

In recent decades, EVs have re-emerged as key players in cell-to-cell and tissue communication, opening new fields of biomedical research, as they have been implicated both in normal physiological processes and in disease progression (1). Particularly in recent years, multiple functions of these vesicles have been described in the onset and development of metabolic diseases, including **obesity** and its comorbidities, with **T2DM** being the most notable (2). T2DM is a chronic metabolic disease characterized by persistently elevated blood glucose due to insulin resistance in peripheral tissues and/or insufficient insulin secretion caused by the progressive death of pancreatic β cells, in which chronic systemic inflammation resulting from obesity and sedentary lifestyle also plays a role. Consequently, diabetes has a significant impact on public health since its incidence and prevalence are rising worldwide.

## EXTRACELLULAR VESICLES FROM ADIPOSE TISSUE AND THEIR ROLE IN DIABETES

Excess fat accumulation in **adipose tissue** during the development of obesity is considered one of the main risk factors for diabetes. The dysfunction of this tissue is closely related to mechanisms associated with this disease, such as the development of **insulin resistance** (diabetes), **inflammation, and the release of fatty acids**. But do EVs participate in these processes? Evidence shows that during the development of obesity, energy-storing cells (adipocytes) in adipose tissue release EVs that interact with neighboring healthy cells, inducing or worsening the disease by themselves (3,4). It has been described that vesicles secreted by cells of obese adipose tissue promote lipid (fat) accumulation and induce insulin resistance (diabetes) in otherwise healthy cells of the same tissue (4). Furthermore, it has been observed that EVs released by adipocytes from obese individuals can interact with other cells present in adipose tissue. Specifically, EVs from adipocytes of obese individuals can interact with immune cells such as macrophages and lymphocytes that infiltrate fat during this disease (5). This interaction promotes their inflammation, thereby triggering the release of pro-inflammatory signals responsible not only for local inflammation but potentially for systemic inflammation as well. In humans, adipocytes in visceral fat (located in the abdomen around organs), which is considered more harmful, release EVs with a higher inflammatory capacity than those from subcutaneous fat (located beneath the skin) (5,6). This chronic low-grade inflammation associated with obesity is known to interfere with insulin signaling, glucose metabolism, and lipid homeostasis, all of which contribute to insulin resistance and diabetes. Therefore, EVs are thought to play an important role in the development of insulin resistance promoted by inflammation. Experimental evidence indicates that EVs establish a dynamic dialogue between adipocytes and macrophages in adipose tissue, participating in the inflammatory process mentioned above. »

**EXTRACELLULAR VESICLES RELEASED BY ALL CELLS OF THE BODY ARE POSTULATED AS TRUE CELLULAR TROJAN HORSES, PARTICIPATING IN BOTH NORMAL PHYSIOLOGICAL PROCESSES AND DISEASE**

EXTRACELLULAR VESICLES EMERGE AS NEW RELEVANT FACTORS IN DIABETES, ACTIVELY PARTICIPATING IN BOTH β-CELL DYSFUNCTION AND INSULIN RESISTANCE

» Additionally, studies show that macrophages also release EVs that may induce insulin resistance in nearby adipocytes.

Of note, adipose tissue EVs do not only act locally but can also enter the bloodstream and interact with other organs and tissues, contributing to insulin resistance and inflammation elsewhere. It has been reported that EVs released by pathological adipocytes in mice, or by visceral and subcutaneous fat from obese human patients, induce insulin resistance in liver hepatocytes, especially those coming from centrally accumulated visceral fat (5).

## EXTRACELLULAR VESICLES FROM THE LIVER IN DIABETES

**Liver**-derived EVs play an important role in the development and progression of diabetes. These EVs, released by different liver cells, can alter insulin signaling and increase insulin resistance (7). In **obesity-related non-alcoholic fatty liver disease** (NAFLD), as in adipose tissue, liver EVs can promote inflammation by activating macrophages and releasing pro-inflammatory cytokines. This inflammation contributes to insulin resistance and further liver damage. Moreover, these hepatic vesicles can alter the function of endothelial cells lining blood vessels, contributing to diabetes complications such as cardiovascular diseases. Furthermore, they can travel through the bloodstream to other tissues such as adipose tissue, the pancreas, and muscle, amplifying insulin resistance and contributing to diabetes development. Conversely, recent studies have shown that liver EVs under normal, non-pathological conditions may have therapeutic potential since they act on peripheral tissues to regulate glucose levels after meals (8).

## EXTRACELLULAR VESICLES FROM THE PANCREAS AND DIABETES

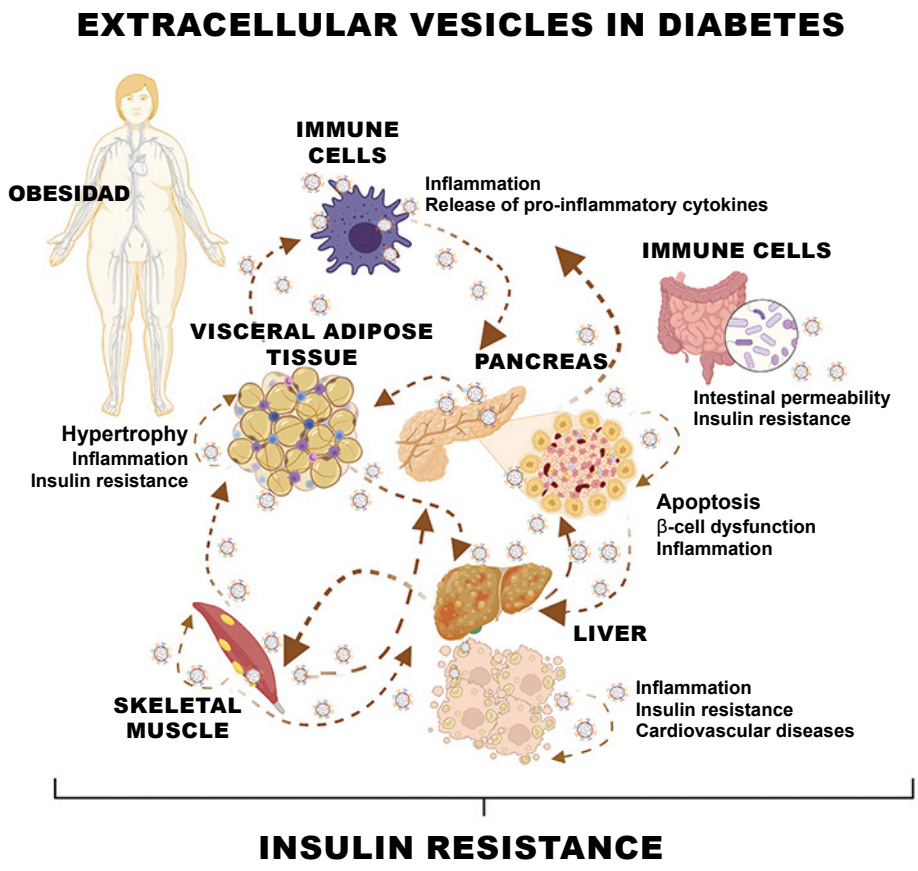
The deterioration of β-cell function or quantity as diabetes progresses is associated with a complex communication network between pancreatic islet cells and other peripheral cells and tissues. Stress factors associated with diabetes—including pro-inflammatory cytokines, lipid and glucose toxicity, and amyloid protein deposits—can alter the microenvironment of the islets, influencing the molecular cargo of β-cell-derived EVs, thereby causing functional changes (9). Therefore, pancreatic islet-derived EVs play an important role in diabetes pathogenesis by mediating inter-organ communication and influencing β-cell function. For instance, studies suggest that prediabetic pancreatic β cells release EVs containing an inhibitory RNA (miR-29) capable of activating immune system cells and increasing insulin resistance. Later, in advanced stages of diabetes, EV-mediated communication between pancreatic islets and other tissues can lead to β-cell apoptosis and dysfunction. Moreover, it has been described that vesicles released by β cells treated with LDL cholesterol can impair insulin signaling and provoke insulin resistance in the liver. Similarly, EVs from fatty liver can increase immune cell infiltration in the pancreas and subsequent β-cell failure.

In summary, the pancreas is the organ affected by diabetic damage and the source of pathogenic EVs that facilitate communication between the pancreas, distant organs, and the immune system. Therefore, EVs originating from or targeting pancreatic islets can influence the physiological regulation of β-cell homeostasis as well as physiological or pathological stress responses.

## EXTRACELLULAR VESICLES FROM OTHER TISSUES AND ORGANISMS

Skeletal **muscle** plays a crucial role in maintaining glucose levels; thus, insulin resistance in this tissue is a key factor in diabetes. It has been demonstrated that regular exercise reduces the incidence of T2DM and that the interaction between skeletal muscle and β cells is essential for this effect. Indeed, EVs released by skeletal muscle after exercise have positive effects on the pancreas (2). In the context of lipid-induced insulin resistance, EVs originating from skeletal muscle cells are loaded with saturated fatty acids and can reach insulin-responsive tissues such as the pancreas and liver, revealing a new form of inter-organ communication and metabolic balance.

As for other organisms, it is increasingly evident that gut **microbiota** imbalance significantly contributes to diabetes by producing abnormal intestinal metabolites and altering intestinal permeability (10). Mou- »




» se studies suggest that EVs released by a beneficial gut bacterium *(Akkermansia muciniphila)* could prevent insulin resistance by counteracting harmful effects on gut permeability caused by a high-fat diet. Generally, intestinal barrier dysfunction associated with obesity and diabetes leads to increased bacterial EVs circulating throughout the body, exacerbating insulin resistance. D

## CONCLUSIONS

Extracellular vesicles released by all body cells are postulated as true cellular Trojan horses, participating in both normal physiological processes and disease. Specifically, EVs emerge as new relevant factors in diabetes, actively contributing to both β-cell dysfunction and insulin resistance. Moreover, under pathological conditions such as obesity, various peripheral organs—such as adipose tissue, muscle, and liver—release their own EVs capable of interacting with the pancreas and altering pancreatic cell function. Conversely, EVs from non-pathological cells exert beneficial effects and are emerging as promising therapeutic tools.

## REFERENCES:

**1.** Qisong L, Jianghong H, Jiang X, Yujie L, Guangheng L. Tracking tools of extracellular vesicles for biomedical research. Front Bioeng Biotechnol. 2022;18 (10):943712.
**2.** Zhang M, Wang L, Chen Z. Research progress of extracellular vesicles in type 2 diabetes and its complications. Diabetes Med. 2022; 39: e14865.
**3.** Zhang B, Yang Y, Xiang L, Zhao Z, Ye R. Adipose-derived exosomes: A novel adipokine in obesity-associated diabetes. J Cell Physiol. 2019; 234:16692–702.
**4.** Camino T, Lago-Baameiro N, Bravo SB, Sueiro A, Couto I, Santos F, et al. Vesicles shed by pathological murine adipocytes spread pathology: characterization and functional role of insulin resistant/hypertrophied adiposomes. Int J Mol Sci. 2020; 21:2252.
**5.** Lago-Baameiro N, Camino T, Vazquez-Durán A, Sueiro A, Couto I, Santos F, et al. Intra and inter-organ communication through extracellular vesicles in obesity: functional role of obesesomes and steatosomes. J Transl Med. 2025;23(1):207.
**6.** Camino T, Lago-Baameiro N, Bravo SB, Molares-Vila A, Sueiro A, Couto I et al. Human obese white adipose tissue sheds depot-specific extracellular vesicles and reveals candidate biomarkers for monitoring obesity and its comorbidities. Transl Res. 2022; 239:85-102.
**7.** Liu Z, Yin R, Tian J. Extracellular vesicles: mechanisms and prospects in type 2 diabetes and its complications. Front Endocrinol. 2025 17; 15:1521281.
**8.** Miotto PM, Yang C-H, Keenan SN, De Nardo W, Beddows CA, Fidelito G et al. Liver-derived extracellular vesicles improve whole-body glycemic control via inter-organ communication. Nature Metabolism. 2024; 6(2):1-19.
**9.** Wei J, Wang Z, Han T, Chen J, Ou Y, Wei L et al. Extracellular vesicle-mediated intercellular and interorgan crosstalk of pancreatic islet in health and diabetes. Front Endocrinol. 2023; 25:14:1170237.
**10.** Barathan M, Luan Ng S, Lokanathan Y, Hwei Ng, Law JX. The profound influence of gut microbiome and extracellular vesicles on animal health and disease. Int J Mol Sci 2024;25(7):4024.