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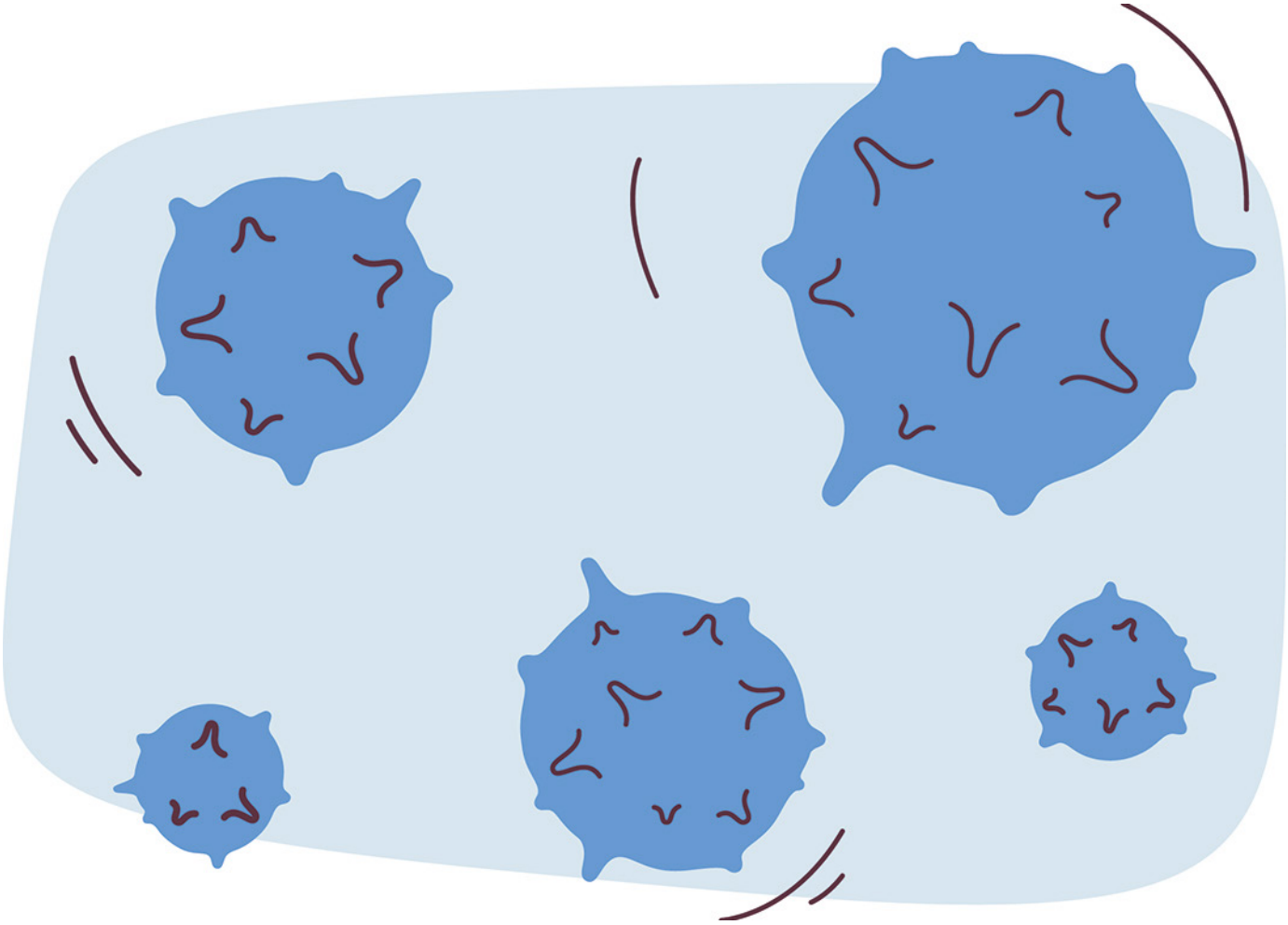


Extracellular vesicles in blood and their relationship with cardiovascular risk in type 2 diabetes

When our cells are under stress, they release different molecules that act as a signal to inform neighboring or distant cells that something is wrong. We used to think that these molecules were released in their free form, but in recent decades, the scientific community has discovered that these signals can also be released in packaged form, contained within extracellular vesicles

Extracellular vesicles are like tiny "bubbles" (between 30 and 1000 nanometers), which carry information from the cell that releases them. This information is selective; that is, depending on the moment or situation in which the cell finds itself, it packages different molecules inside the vesicles. This is why extracellular vesicles carry very valuable information about the "health status" of their cell of origin. In other words, extracellular vesicles are like a personal letter written by the cell to a specific recipient, as opposed to the release of free molecules, which could be likened to mass commercial mail.

Extracellular vesicles are distinguished by various characteristics. They can be generated by the invagination of the cell membrane (which generally results in medium-sized vesicles – between 100 nm and 500 nm, more or less). These are called microvesicles. They can also be generated by the fusion of multivesicular intracellular bodies with the cell membrane, which tend to be smaller (30 nm up to 100 nm). These are called exosomes. When the cell undergoes programmed cell death, it also breaks down into apoptotic bodies, which are the largest type of extracellular vesicle (500 nm up to 1000 nm). All extracellular vesicles, regardless of the cell that releases them or their formation mechanism, are composed of lipids, genetic material such as messenger RNA (mRNA), microRNA (miRNA), or even small amounts of DNA, and proteins such as transcription factors, cytokines, and growth factors. Together, these elements make up the message in the letter written by the cell ***(Figure 1)***.

Recently, the term "liquid biopsy" has been gaining traction. It refers to collecting bodily fluids (blood, urine, sputum, and even sweat or tears) using non-invasive or minimally invasive methods, to "tell" us about the person's health status (1). In this regard, various research groups, many of them part »

THE CONCENTRATION OF EXTRACELLULAR VESICLES FROM LEUKOCYTES, PLATELETS, AND ENDOTHELIAL CELLS IN THE BLOOD IS INCREASED IN PEOPLE WITH TYPE 2 DIABETES AND REFLECTS THE DURATION AND SEVERITY OF THE DISEASE

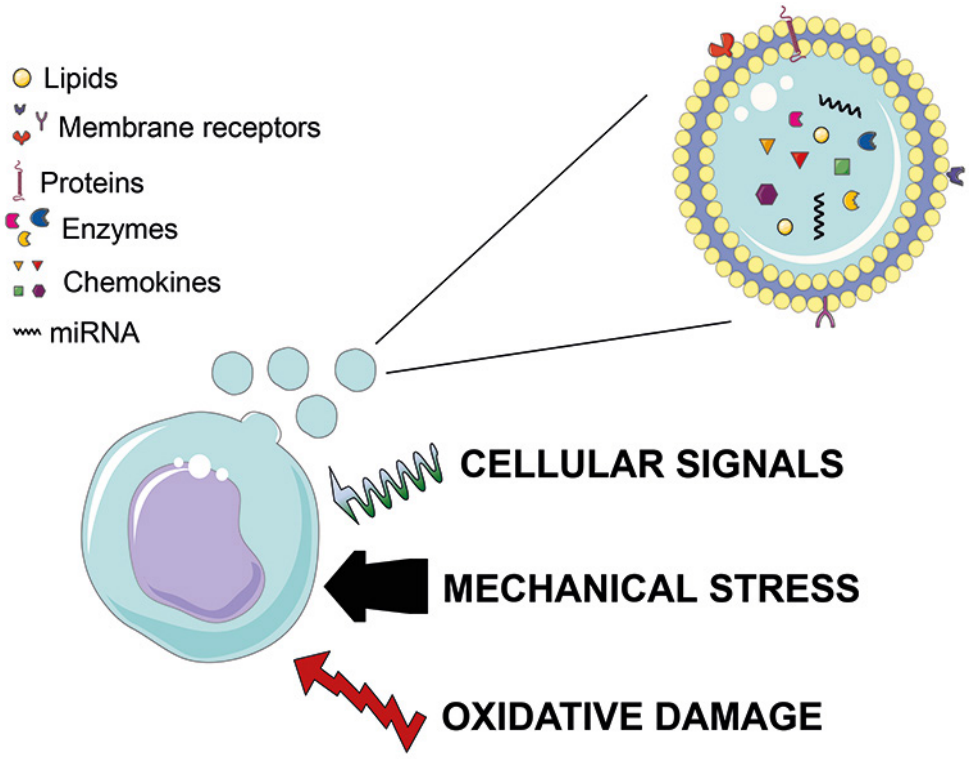
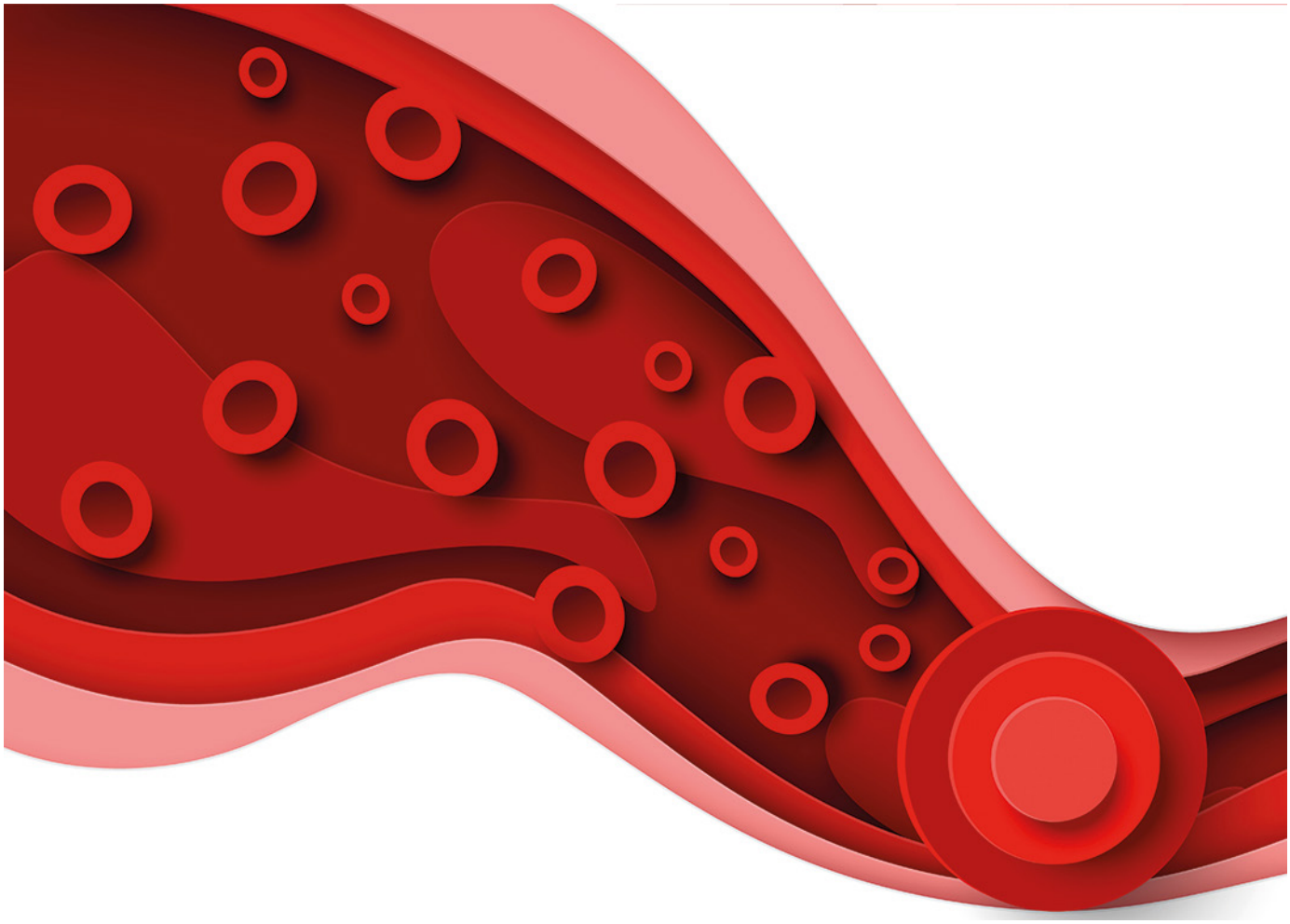


FIGURE 1. Formation of extracellular vesicles (adapted from reference 1).



» of Geivex – the Spanish Group for Innovation and Research in Extracellular Vesicles **(https://www.geivex.org/)**, have been investigating how extracellular vesicles in bodily fluids can help predict long-term diseases. This is because extracellular vesicles released into the bloodstream can travel both locally and systemically, affecting cells in other parts of the body (i.e., these cells read the letters and act according to the message).

A few years ago, we observed that people with type 2 diabetes had higher levels of extracellular vesicles in their blood compared to people with a similar cardiovascular risk but without diabetes (2). More specifically, we observed that leukocytes, platelets, and endothelial cells in people with diabetes release more medium-sized extracellular vesicles (microvesicles) into the bloodstream. Furthermore, the levels of these vesicles in the blood increase over time, so people with longer courses of the disease have higher levels of these vesicles compared to those with more recent onset. Therefore, this gives us a clue that the concentration of these vesicles in the blood could be a marker of the severity of diabetes. In this context, we recently observed that people with obesity and type 2 diabetes have significantly higher levels (even more than double) of extracellular vesicles released by platelets, leukocytes, and endothelial cells, and of vesicles with prothrombotic potential, compared to obese individuals without type 2 diabetes, who also have much higher levels of these vesicles than people without obesity or type 2 diabetes (3). Moreover, blood concentrations of vesicles released by platelets, leukocytes, and endothelial cells, as well as blood concentrations of vesicles with prothrombotic potential, directly correlate with the level of peripheral insulin resistance (measured by the HOMA and Matsuda indices) and with the severity of hyperglycemia.

As is well known, type 2 diabetes—beyond insulin resistance and hyperglycemia—is also characterized by a general proinflammatory state, hypercoagulability, and dyslipidemia. These conditions »

EXTRACELLULAR VESICLES CONTAIN HIGHLY VALUABLE INFORMATION ABOUT THE "HEALTH STATUS" OF THEIR CELL OF ORIGIN.

» are extremely harmful to the vascular endothelium, as they accelerate the development of microvascular disorders, atherosclerosis, and coronary artery disease. In a group of patients with coronary artery disease and type 2 diabetes, we observed that those who had albuminuria, and therefore a more severe or advanced state of diabetes, also had higher blood levels of extracellular vesicles released by endothelial cells, monocytes, and platelets (4). In fact, concentrations of vesicles derived from endothelial cells could, also, independently predict albuminuria, reflecting greater chronic activation of endothelial cells in the more advanced stages of diabetes when albuminuria occurs.

In conclusion, the concentration of extracellular vesicles in the blood derived from leukocytes, platelets, and endothelial cells is increased in people with type 2 diabetes and reflects the course and severity of the disease. Since we have different diagnostic and prognostic methods for type 2 diabetes, one might ask what role these vesicles play in diabetes. Well, it turns out that these elevated levels of cell-derived vesicles from the vascular compartment have a direct relationship with cardiovascular event risk factors and predict long-term heart attacks (1). In fact, blood concentrations of extracellular vesicles released by platelets, leukocytes, and endothelial cells increase with each cardiovascular risk factor and in an additive manner. This happens because extracellular vesicles actively participate in all stages of the onset and progression of atherosclerosis, as well as in the formation of clots that lead to cardiovascular events (i.e., heart attack) (5). It has even been shown that the prothrombotic activity of some extracellular vesicles is 50 to 100 times greater than the procoagulant capacity of activated platelets (6), which are the main culprits in clot formation.

On the other hand, and again conditioned by the context and stimulus that triggers their secretion, some extracellular vesicles can have protective biological functions, perhaps as a compensatory mechanism or even with potential reparative or regenerative properties, making the study of extracellular vesicles an exciting field full of clinical possibilities. In this regard, GEIVEX (https://www.geivex.org/) organizes annual courses where the latest advances in research and applications of extracellular vesicles can be seen, not only in the field discussed in this article.

Of note, however, that the implementation of extracellular vesicles as biomarkers in clinical practice still needs to overcome some barriers, such as the development of standardized and reproducible techniques.

Nevertheless, in the coming future, liquid biopsies of extracellular vesicles could become a quantitative non-invasive method with insignificant risk for the patient. People with diabetes have a higher risk of cardiovascular disease, so monitoring their blood levels of vesicles could help personalize a more appropriate evaluation and preventive intervention based on their actual cardiovascular risk, helping both to reduce their risk and to delay the progression of cardiovascular disease, thereby delaying or avoiding a possible heart attack. D

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