



Simple method to assess the risk of vascular inflammation for diabetes patients

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A team of international researchers from Nanyang Technological University, Singapore (NTU Singapore), Tan Tock Bed Hospital (TTSH) in Singapore and the Massachusetts Institute of Technology (MIT) have developed a simple method to extract small biological particles from a person's blood and use them as biomarkers to assess the health of their blood vessels.

The biomarkers are nanoscale particles called extracellular vesicles (EVs) that are released by specific cells in the bloodstream. Their job is to transport biomaterials, such

as proteins and nucleic acids, from one cell to another.

In a paper published in June 2021 in *Royal Society of Chemistry – Lab on a Chip* the team showed that the blood samples from several diabetic patients had an abnormally high amount of circulating EVs secreted by immune and platelet cells (10 to 50 times more) compared to other diabetic patients.

The team found in laboratory experiments that when these EVs (taken from the six patients with high EVs) were added to vascular cells, they induced higher levels of vascular inflammation markers. The results suggest that patients with high EVs in the blood may be at higher risk of developing vascular complications in the long term.

The results were reported by an interdisciplinary team led by Assistant Professor Hou Han Wei from the School of Mechanical and Aerospace Engineering and NTU President Professor Subra Suresh in collaboration with NTU Materials Science and Engineering Assistant Professor Dalton Tay, Associate Professor Rinkoo Dalan, Senior Consultant, Endocrinology, TTSH and MIT Senior Researcher and NTU Visiting Professor, Dr Ming Dao.

In their research paper, the team explained how their prototype 'lab-on-a-chip' can automatically separate electric cars from blood tests in an hour – about one-fifth of the usual time required by conventional centrifugation methods.

This is how the new chip works

Named "ExoDFF" (Exosome Isolation Using Dean Flow Fractionation), the microfluidic chip first sends a blood sample through a high-speed helical duct.

Based on centrifugal and inertial effects – the motion of the fluid and the hydrodynamic forces acting on particles in the fluid – larger blood cells are centrifuged in one direction, while the smaller EVs flow faster and are directed to a different outlet for collection.

The current global benchmark for separating electric cars from blood using ultracentrifugation is time consuming (up to five hours) and captures very few electric cars from the blood test. It is also cumbersome and non-standardized as different laboratories have different protocols for extraction and cleaning of electric cars.

By comparison, the ExoDFF chip uses the process of EV separation and enrichment to be combined into a single step and does not require trained expertise, said Asst Prof Hou, also a faculty at NTU's Lee Kong Chian School of Medicine.

"We worked closely with our TTSH clinic partner to ensure that one-step operation of the chip is all that is needed to easily extract the EVs for analysis. Microfluidics is now a mature technology, and with our deep expertise in this area, we can easily design unique microfluidic solutions to isolate various cells and biomarkers from human blood," says Asst Prof Hou, who previously invented a laboratory on a chip to analyze a person's immune system status in 2019.

Potential impact of innovation

Over 422 million people in the world have diabetes, and in Singapore 10 percent of the population (over 400,000) have the metabolic disease, while cardiovascular disease accounts for approx. 31% of deaths worldwide, including Singapore.

Assoc Prof Rinkoo Dalan, who is also an adjunct professor at the Lee Kong Chian School of Medicine, said: "Cardiovascular disease (CVD) accounted for 18.6 million deaths worldwide in 2019, of which 58% occurred in Asia. Despite significant Progress in treatment, mortality and disease associated with atherosclerosis remains high. "

"We need methods to categorize the potential risk for our diabetes and other high-risk patients long before significant arterial damage has occurred so that we can introduce preventative methods. This innovation has the potential to detect the risk early so that preventive methods can help. then in limiting the progression of damage to the blood vessels.

"This innovation is particularly beneficial as it coincides with the development of new anti-inflammatory drugs such as canakinumab, which have the potential to prevent cardiovascular disease in these patients, as well as other diabetes-specific drugs such as SGLT2 inhibitors, which may "certain protective effects on the heart. These drugs can then be given to patients who have been shown to have a higher risk of developing CVD. The device also has the potential to be used to assess the effect of therapy on the arteries."

Being able to identify diabetic patients who have increased vascular inflammation can give physicians a head start in treating cardiovascular disease in its early stages before it develops into a more serious condition that requires more invasive treatment with stents or surgery.

Prof Subra Suresh, Distinguished University Professor at NTU

Currently, the EV separation chip can process up to 5 ml of blood in one hour. Since the ExoDFF design is scalable, inexpensive (each chip costs only a few dollars to manufacture) and does not require chemicals, it can be designed to process larger sample volumes or adapted for use in the manufacture of cell-based or EV-based therapies, such as stem cell therapy.

The team hopes to develop an automated and smaller 'printer size' version of the machine for clinical and research use.

The team also plans to perform several experiments on a larger sample group of patients to further validate their hypothesis of using EVs as non-traditional biomarkers for risk stratification of diabetic patients.

Source:

[Nanyang University of Technology](#)

Journal reference:

Tay, HM, *et al.* (2021) Direct isolation of circulating extracellular vesicles from blood for vascular risk profiling in type 2 diabetes mellitus. *Lab Chip*.
doi.org/10.1039/D1LC00333J.

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