Study finds estrogen deficiency affects systemic signaling in response to exercise

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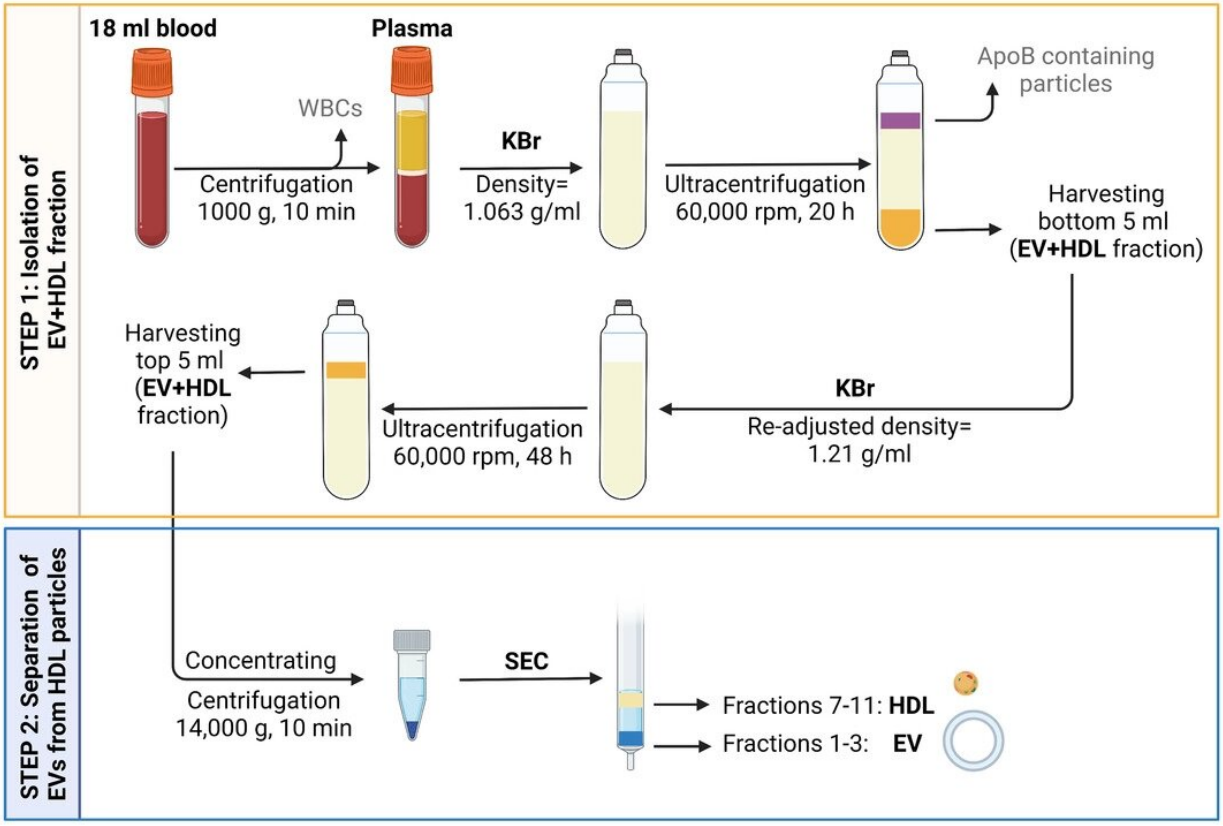

Flowchart of the two-step isolation protocol of EV and HDL particles. STEP 1: isolation of EV+HDL fraction (based on density) and STEP 2: separation of EVs from HDL particles (based on size). Credit: *Journal of Extracellular Vesicles* (2023). DOI: 10.1002/jev2.12308

Menopause is associated with unfavorable changes in health that physical activity alone cannot counteract. Currently we lack the knowledge why even a relatively high vigorous physical activity level does not diminish the negative effects of menopause in, for example, blood lipid levels.

A study conducted at the University of Jyväskylä (Finland) examined whether the body reacts to exercise differently when there is an estrogen deficiency or if estrogen was obtained from estrogen-based hormonal therapy. The study revealed that estrogen deficiency affects the systemic signaling in response to exercise. The results are published in the *Journal of Extracellular Vesicles*.

Menopause leads to estrogen deficiency, which is associated with an increase in metabolic and cardiovascular diseases. Previous studies conducted at the University of Jyväskylä have revealed that even though physical activity helps maintain healthier body composition, even a relatively high level of physical activity does not diminish the negative changes in health caused by menopause. However, it has not been studied whether estrogen deficiency can affect the systemic response to exercise.

"We investigated the effect of estrogen deficiency on two signaling molecules in blood circulation; extracellular vesicles (EV) and high-density lipoprotein (HDL) particles," says Academy of Finland postdoctoral researcher and the principal investigator of the ErROR-study Sira Karvinen from the Gerontology Research Center, Faculty of Sport and Health Sciences, University of Jyväskylä, Finland.

"EVs are membrane-bound transport vehicles sent by cells, which are used in communication between tissues. The best-known function of HDL particles is the reverse cholesterol transport, by which the body removes excess cholesterol from peripheral tissues. Recent studies have shown that HDL particles can also act as inter-tissue messengers."

Eighteen postmenopausal women participated in the study, half of whom used estrogen-based hormone replacement therapy. To induce systemic response to exercise, the women conducted a maximal oxygen uptake test on a bicycle ergometer. Blood plasma samples were taken before and after the exercise test and the samples were analyzed to observe if exercise affects the number of messenger molecules carried via EVs or HDL particles.

"Our study is the first in which the messenger molecule content carried via EV and HDL particles have been accurately compared to each other and showed differences between these two signal carriers," explains the principal investigator of the EsmiRs study, associate professor Eija Laakkonen. "When we studied the contents of the messenger molecules in samples taken before and after exercise, we found that the contents change in response to exercise in both EV and HDL particles.

"A significant new discovery was that the use of hormone replacement therapy affected the body's communication. It is a subject of further research whether this unresponsiveness to exercise in estrogen deficient women has wider health effects. Exercise typically causes clear changes in the amount of micro-RNA molecules in the blood, as we have previously shown.

"Based on our new results, the estrogen level affects exercise-induced signaling in EV and HDL particles and can affect the metabolism of postmenopausal women during exercise via micro-RNA molecules. It is possible that the differences in systemic communication in response to exercise is part of the reason why vigorous exercise is not enough to diminish the negative changes in health associated with menopause."

More information: Sira Karvinen et al, Extracellular vesicles and high-density lipoproteins: Exercise and oestrogen-responsive small RNA carriers, *Journal of Extracellular Vesicles* (2023). DOI:

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