Could targeting metabolism treat blood clots in antiphospholipid syndrome?

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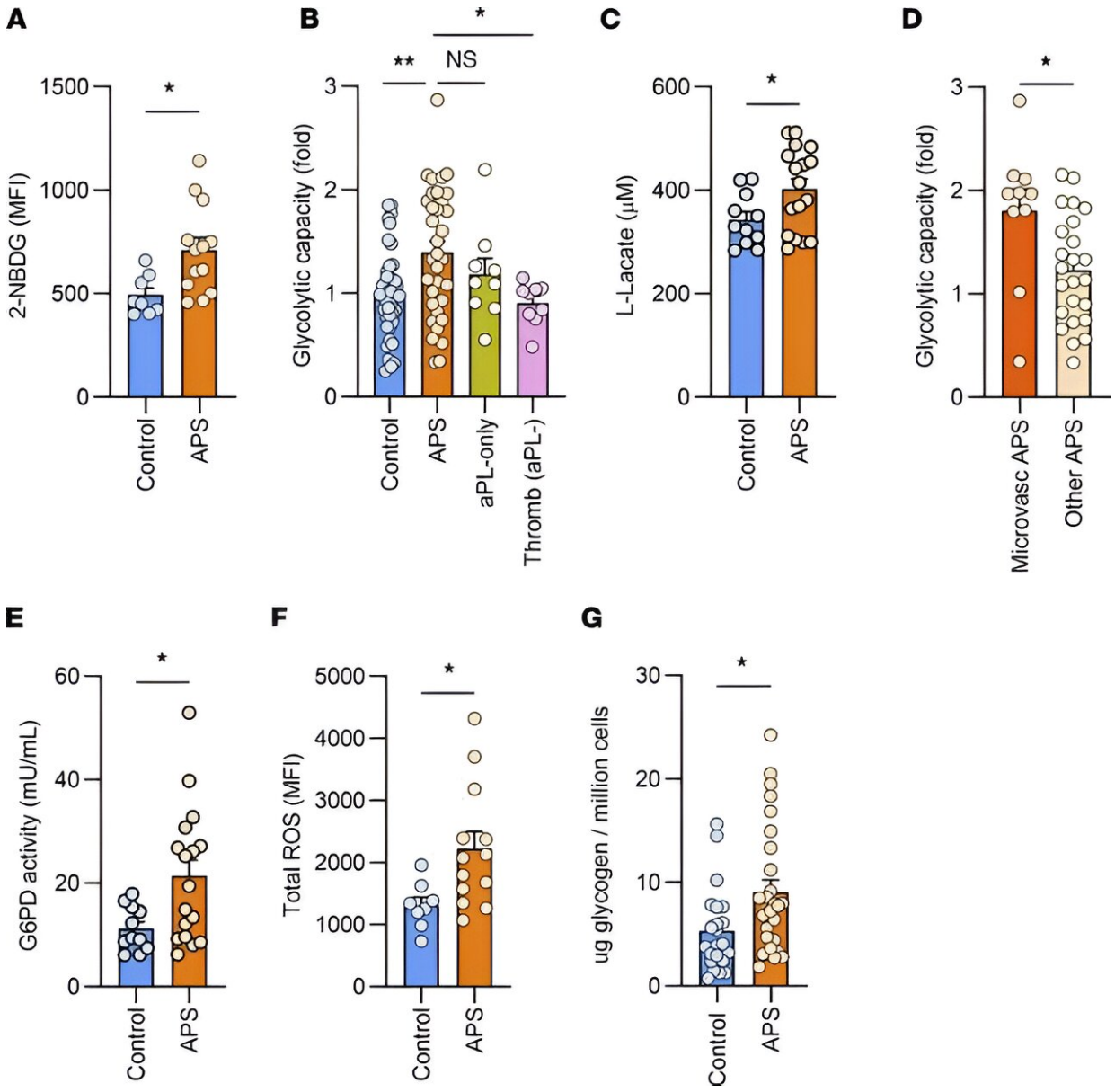

Metabolic parameters in neutrophils from people in the control group, patients with APS, patients with aPL-only, and patients with Thromb (aPL–). Credit: *Journal of Clinical Investigation* (2024). DOI: 10.1172/JCI169893

Neutrophils are an important type of white blood cell that help your immune system fight infections. One of the many ways neutrophils help is by capturing germs in sticky, spider web-like structures called neutrophil extracellular traps, or NETs. However, excessive formation of NETs is seen in many autoimmune diseases as a sign of exuberant inflammation.

In the autoimmune disease known as antiphospholipid syndrome, this inflammation causes blood clots, strokes and miscarriages. Antiphospholipid syndrome is usually treated with blood thinners that patients take for the rest of their lives.

Unfortunately, blood thinning medicines don't prevent future blood clots in all patients with the disease. Blood thinners also have important side effects to be aware of, such as major bleeding. Patients with antiphospholipid syndrome need better treatments, especially ones with fewer side effects.

One promising approach is to target neutrophils and NETs.

A research team at University of Michigan Health led by Ajay Tambralli, M.D., a clinical assistant professor in both adult and pediatric rheumatology, is investigating how metabolism—the process by which cells turn sugars, fats and proteins into energy—is used to make NETs. They're also using this knowledge to develop treatments based on metabolism to lower the propensity of neutrophils to make NETs in APS.

The work is published in the *Journal of Clinical Investigation*.

The team's study found neutrophils from antiphospholipid syndrome patients use a metabolic process called glycolysis more aggressively than neutrophils from healthy people. Glycolysis converts sugars into energy and generates by-products used for different purposes in the cell.

The authors found that one such by-product called glucose-6-phosphate feeds into another metabolic process known as the pentose phosphate pathway. The pentose phosphate pathway then arms the neutrophils to make NETs.

"When we disrupted either glycolysis or the pentose phosphate pathway, neutrophils made fewer NETs. Fewer NETs meant smaller blood clots in our model systems," said Tambralli.

Promisingly, they also found that this strategy didn't increase bleeding.

"These findings are an important step to better understanding how metabolism is altered in APS," Tambralli added.

Armed with this knowledge, the research team has begun investigating the underlying causes of the metabolic alterations in antiphospholipid syndrome.

"We want to gain a clearer picture of what is driving the increase in glycolysis, which can then be harnessed to develop metabolism-focused treatments for APS," said Tambralli.

Though more research is needed, the goal is to bring such treatments to patients with antiphospholipid syndrome and, potentially, other diseases where NETs cause blood clotting.

"Part of the treatment regimen might be adjusting how someone eats, 'putting neutrophils on a diet,' if you will. We have some ideas on this front that we will test in our next manuscript. The goal is to keep the neutrophils healthy for fighting infections but stopping the excessive NETs that lead to blood clots."

The hope is to make strategic treatment decisions to address the root causes of antiphospholipid syndrome for each individual patient.

More information: Ajay Tambralli et al, Neutrophil glucose flux as a therapeutic target in antiphospholipid syndrome, *Journal of Clinical Investigation* (2024). DOI: 10.1172/JCI169893

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