Study shows gut microbes alter platelet function, heightens risk of heart attack and stroke

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In a combination of both clinical studies of over 4,000 patients and animal model studies, Cleveland Clinic researchers have demonstrated -- for the first time -- that gut microbes alter platelet function and risk of blood clot-related illnesses like heart attack and stroke.

When the nutrient choline -- which is abundant in animal products like meat and egg yolk -- is ingested, gut microbes play a role in breaking it down and producing the compound TMAO. High levels of TMAO have been linked to heart disease in recent studies. The studies showed that blood TMAO levels are associated with heightened risk of heart attacks and strokes in humans, even after adjusting for traditional cardiac risk factors, renal function, markers of inflammation, medication use, and cardiovascular disease status.

The new study -- to be published in *Cell's* March 10, 2016 online edition and March 24 print edition -- shows that TMAO directly alters platelet function, increasing thrombosis (blood clot) potential, which could potentially be the mechanism by which TMAO increases heart attack and stroke risk. These findings reveal a previously unrecognized mechanistic link between specific dietary nutrients, gut microbes, platelet function, and thrombosis risk.

"It is remarkable that gut microbes produce a compound that alters platelet function and thrombotic heart attack and stroke risk," said lead author Stanley Hazen, M.D., Ph.D., chair of the Department of Cellular & Molecular Medicine in the Lerner Research Institute and section head of Preventive Cardiology & Rehabilitation in the Miller Family Heart & Vascular Institute at Cleveland Clinic "This new link helps explain how diet-induced TMAO generation is mechanistically linked to development of lethal adverse complications of heart disease. The results of the studies suggest potential new therapeutic targets and possible nutritional interventions for preventing cardiovascular events and improving heart health."

This latest discovery further adds to the growing body of data showing a link between TMAO, gut microbes, and heart disease. It also shows that lowering TMAO may represent a potential new way to reduce the formation of blood clots, and therefore decrease the risk of cardiovascular events like heart attacks and strokes. Heart disease is the No. 1 killer in the world of both men and women.

The link between TMAO, gut microbes and heart disease was first discovered five years ago by the same investigative team, led by Dr. Hazen. Weifei Zhu, Ph.D., and Jill Gregory,Ph.D. are co-first authors on the current manuscript, and are also members in the Department of Cellular & Molecular Medicine in the Lerner Research Institute.

In this study, researchers analyzed blood levels of TMAO in over 4,000 patients and saw a significant correlation between higher TMAO and thrombosis potential. This generated the hypothesis that TMAO may directly impact platelet function. Subsequent studies with both human platelets and animal models confirmed that TMAO makes platelets over-reactive, heightening thrombosis potential and accelerating clotting rates. Enhanced platelet responsiveness and clot formation is the culminating event that causes a heart attack or stroke, which account for the majority of deaths worldwide.

"We have shown that TMAO fundamentally alters calcium signaling within platelets; when TMAO is elevated, platelet responsiveness to known triggers like thrombin, collagen or ADP is heightened," Hazen said. "In general, there's a broad range for how quickly different people will form clots. However, across the board, when TMAO is elevated, platelet responsiveness jumps to the hyper-reactive side of normal."

Microbial transplantation studies showed TMAO production and thrombosis potential are transmissible traits, building on the recent demonstration that atherosclerosis susceptibility similarly can be transmitted from donor to recipient with transfer of gut microbes via TMAO production potential.

Source:
Cleveland Clinic
