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Study finds statin use linked to rare autoimmune muscle disease

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Taking statins, they found, can sometimes cause the body to produce antibodies against its own proteins, creating a condition that gets progressively worse — not better — even after the medication is discontinued. As the painful and debilitating disorder is uncommon and can be treated with steroids and other immune-suppressing drugs, the Hopkins researchers caution that people who must be on statins to reduce serious risk of heart disease and stroke should not avoid the drugs.

“We have long known that there must be environmental triggers to the development of autoimmune disorders,” says Andrew L. Mammen, M.D., Ph.D., an assistant professor of neurology and medicine at the Johns Hopkins University School of Medicine. “Now we have evidence that this medication is just such a trigger and, under certain circumstances, provokes a sustained autoimmune disease.”

Beyond the "proof of principle" in Mammen's findings, published online in the journal *Arthritis & Rheumatism*, they could also lead to lab tests that identify early autoimmune muscle disease, guide treatment before symptoms escalate and, possibly, predict who is at risk before statins are prescribed.

Mammen cautions that the Hopkins research describes a rare side effect, noting that statins are a "fantastic medication" that have proven value. "No one who needs statins should be afraid to take them because of the slim risk of developing this autoimmune disease," he says.

"Statins save a huge number of lives. They dramatically reduce the risk of strokes and heart attacks," Mammen adds. "The ultimate goal of our research is to determine before patients start taking statins who might be sensitive to the medication and who might be susceptible to its potentially toxic effects on the muscle. We want to prevent this autoimmune disease."

Although statins are tolerated by most patients, about 5 percent who take them experience muscle pain and/or weakness severe enough to warrant stopping the medication. Most of those people will make a full recovery once they are off the drug, but there appears to be a group who will develop this progressive autoimmune muscle disease. They get weaker even after the medication is stopped, some end up in wheelchairs and at least one has died. Immunosuppressive therapy with steroids or other drugs are effective in reversing the disease in most patients, Mammen says.

In his initial research, Mammen and his colleagues focused on 26 patients at the Johns Hopkins Myositis Center with necrotizing myopathy, a muscle-wasting disorder with no known cause. Sixteen were found to have a previously unknown antibody. Of the 16 patients with this novel antibody, 12 were over the age of 50 and, of those, more than

80 percent had taken statins before their muscle pain and weakness began. The frequency of statin use in patients with similar muscle diseases is significantly lower. In his latest research, Mammen identified the target of the antibodies as HMG-CoA reductase, or HMGCR. HMGCR is the enzyme responsible for making cholesterol — and it is the same enzyme that statins target.

In their collection of over 750 patients with muscle symptoms, 45 patients with HMGCR antibodies were identified. Of those over 50 years of age, greater than 90 percent had a prior statin exposure. The younger patients, he says, had not been on statins, and how the disease is triggered has not been determined. However, Mammen suspects that they may suffer from other cholesterol issues, a factor that could play a role in the development of the disease.

Antibodies are typically made by healthy people to recognize and destroy foreign invaders. But in patients with autoimmune diseases, the body makes auto-antibodies — antibodies that attack the body's own proteins. In the case of statin-associated autoimmune muscle disease, the body attacks its own HMGCR. When a patient takes statins, HMGCR levels rise as the body tries to compensate for the reduction in the enzyme caused by the medication. Mammen hypothesizes that the extra HMGCR in the body may sometimes stimulate the immune system to make autoantibodies.

Compounding the problem is the finding that while normal muscle tissue makes low levels of HMGCR, regenerating muscle cells make very high levels of HMGCR. This suggests that once the autoimmune muscle disease process is initiated by statin use, high levels of HMGCR in regenerating muscle cells continue to fuel the aggressive and painful autoimmune response, even after statins are withdrawn.

Although doctors don't yet know how many people have statin-

associated autoimmune muscle disease, Mammen and his colleagues believe it is rare. Even in the Myositis Center, just four percent of patients have been diagnosed with it. Mammen says the lab test he and his team have developed, which has not yet been approved by regulators, enables them to diagnose the disease with near certainty.

Some of his patients, however, continue to need the very medication that caused their pain.

“One of the questions that remain is: Can you safely restart statins? It’s important because some of our patients were put on statins for very good reasons, like they’ve had a heart attack,” Mammen says. “We would like to find out if there is a way for these patients to begin taking the medication again.”

Provided by Johns Hopkins University

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