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Fat-cell hormone linked to kidney disease

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Reduced levels of a hormone produced by fat cells and linked to the development of insulin resistance may also be related to a higher risk of kidney disease, according to a study led by researchers at the University of California, San Diego School of Medicine and Thomas Jefferson University. Their study, to be published in the *Journal of Clinical Investigation* on April 22, could point the way to drug therapies that can protect renal and cardiac function in patients with obesity.

The new findings show that the hormone, adiponectin, produced by fat cells, circulates in the blood and acts to both suppress inflammation – known to be a contributor to diabetes and cardiovascular disease – and to reduce protein in the urine.

“A deficiency in adiponectin could be the major reason why obese patients develop the initial signs of kidney disease,” said principal investigator Kumar Sharma, M.D., F.A.H.A., professor of medicine and Director of Translational Research in Kidney Disease at UC San Diego’s School of Medicine. He added that an elevated level of protein in the urine, termed albuminuria, is often seen with obesity. Albuminuria is an indicator of kidney disease and an important risk factor for cardiovascular disease. “At present, the connections between the kidney and the cardiovascular system are not clear. A better understanding of the relationships between the kidney, the cardiovascular system and obesity will be of major benefit in treating these common public health problems at an early stage.”

“The findings in the kidney are consistent with beneficial effects we

reported for adiponectin in the microvasculature, in which it reduces oxidative stress and inflammatory responses," said co-corresponding author Barry J. Goldstein, M.D., Ph.D., professor and director of the Division of Endocrinology, Diabetes and Metabolic Diseases at Thomas Jefferson University in Philadelphia. "In this setting, adiponectin suppresses the adverse effects of high glucose, which implies that it may eventually be shown to serve a protective role in patients with diabetes as well as those with obesity."

A network of fine capillaries in the kidney acts as a filter to prevent proteins in the blood from being secreted into the urine. This filter is made up of three components, one of which – the podocyte cell – serves to regulate albuminuria.

"We discovered that the hormone adiponectin, produced by fat cells, is directly linked to the healthy function of podocytes," said Sharma. In a study of obese patients without obvious diabetes or kidney disease, the research team found that when blood adiponectin levels were low, there was a direct correlation to elevated albumin protein levels in the urine.

Sharma explained that levels of adiponectin hormone are sometimes reduced in obesity. With reduced levels of the hormone, there is an associated loss of the protective effect of adiponectin in the podocytes, leading to an overproduction of inflammatory molecules. In addition, the dysfunctional podocyte allows albumin to enter the urine and may contribute to the overall inflammation occurring in the body.

To explore whether the lower hormone levels were simply an indication of albuminuria or played a causative role in its development, the scientists studied a knockout model of a mouse lacking the adiponectin hormone, and discovered that these mice had high urine albumin levels. Treatment of the mice with adiponectin brought the albuminuria back to normal levels.

They also focused on a receptor on the podocyte cell surface that is associated with a molecular signaling pathway, the AMP kinase enzyme (AMPK), which acts as an energy sensor for the cell and is activated by adiponectin. The research showed that if AMPK is stimulated, either chemically or by introducing adiponectin, the filter works normally to keep albumin from leaking out of the blood and into the urine. However, when there is a lack of adiponectin, the resulting decrease in AMPK activity contributes to dysfunction of the filter. Therefore, the researchers concluded that deficiency of adiponectin is indeed causative to albuminuria.

“We know there are certain medicines that stimulate the AMPK pathway, including adiponectin and a drug called Metformin, which is commonly given to patients with diabetes,” said Sharma. “This study suggests that using the hormone adiponectin, Metformin or other therapies could work to protect kidney function in patients who are obese, even before they have diabetes.”

Last, the researchers looked at markers of inflammation in the kidney that may be regulated by adiponectin, and found that the podocyte also produces an inflammatory enzyme called NOX4 which is increased in the absence of the hormone.

“When you don’t have the hormone there to suppress it, NOX4 enzyme is stimulated and can potentially contribute to the inflammation going on in the kidney and perhaps elsewhere in the body,” said Sharma. Sharma added that replacing the hormone adiponectin in obese patients might work preventively to help the podocytes do their job, thus preventing kidney damage and inflammation.

Source: University of California - San Diego

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