ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

KIDNEY WEEK EDITION

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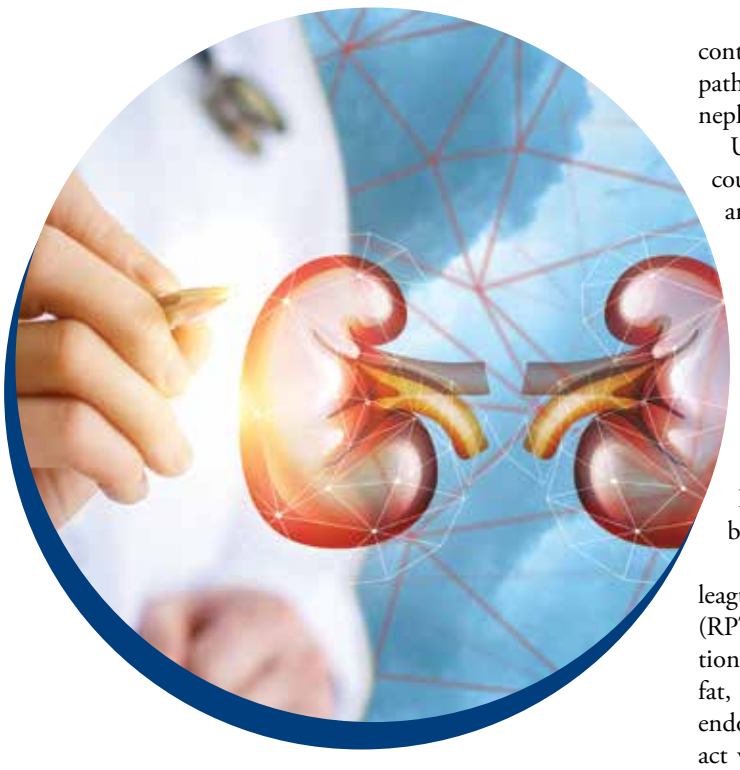
New Research Provides Clues to How Obesity Jeopardizes Kidney Health

By Tracy Hampton



Mounting evidence indicates that obesity has detrimental effects on the kidneys, and recent research is revealing the potential mechanisms involved. A new study published in the *Journal of the American Society of Nephrology* points to the important contribution of the endocannabinoid system to the pathogenesis of obesity-induced renal lipotoxicity and nephropathy.

Up to one-third of kidney disease in the United States could be related to obesity, likely due to hemodynamic and morphologic changes in the kidney.

"Obesity-associated renal structural and functional changes develop early in the course of obesity and the metabolic syndrome, and although multiple metabolic factors—such as insulin, glucose, and leptin—have been proposed to contribute to obesity-associated nephropathy, the underlying pathogenic signaling mechanisms have not been completely elucidated," said Joseph Tam, DMD, PhD, of the Institute for Drug Research at The Hebrew University of Jerusalem, in Israel.

In search of potential insights, Dr. Tam and his colleagues closely examined renal proximal tubular cells (RPTCs), which are responsible for active renal reabsorption and are especially sensitive to the accumulation of fat, an effect called lipotoxicity. Their work focused on endocannabinoids, endogenous lipid ligands that interact with the cannabinoid-1 receptor (CB1R), which is abundantly expressed in the brain and periphery, including the kidney.

When the team fed mice a high-fat diet, animals that lacked expression of the CB1R in RPTCs experienced significantly less obesity-induced lipid accumulation in the kidney as well as less kidney injury. "Using a novel mouse strain that lacks the CB1R from the RPTCs, we were able to demonstrate its pivotal role in the development of renal inflammation, fibrosis, and dysfunction during obesity," said Dr. Tam.

Additional experiments revealed the molecular signaling pathway involved in mediating the CB1R-induced kidney injury and lipotoxicity in RPTCs. Specifically, these deleterious effects associated with decreased activation of liver kinase B1 and the energy sensor AMP-activated protein kinase (AMPK), as well as reduced fatty acid β-oxidation.

"Ultimately, this was a very interesting paper that is building on our understanding of a new metabolic pathway in kidney injury," said Adam Whaley-Connell, DO, who was not part of the study and is a nephrologist and associate professor at the University of Missouri School of Medicine. "There are a number of studies that suggest the endocannabinoid system regulates proximal tubule function from mouse models to humans in diabetes; however, this current paper highlights the pathway may be regulated to a great extent by fat feeding and is an important regulator of lipid accumulation, fatty acid oxidation, and the AMPK mechanism that contributes to fibrosis in the kidney. In the search for new therapeutic targets this paper provides an intriguing new mechanism in obesity and/or diabetic kidney disease."

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According to Dr. Tam, the work provides a novel approach to slow the development of renal injury through chronic blockade of peripheral CB1Rs. "And, it also supports strategies aimed at reducing the activity of the endocannabinoid system, specifically in the kidney, to attenuate the development of RPTC dysfunction in obesity."

Allon Friedman, MD, who was not involved with the work and is a nephrologist and clinical investigator at Indiana University School of Medicine, noted that the intimate connection between rising rates of obesity and chronic kidney disease makes it likely that this topic will become increasingly prominent in the coming years.

"These intriguing animal studies expand our understanding of how endocannabinoid physiology influences kidney health," he said. "The next step will be to extend these findings in humans through the testing of endocannabinoid receptor antagonists." In his 2011 *Kidney News* article, Dr. Friedman pointed to other possible factors, including alterations in levels of adipocyte-related cytokines such as leptin and adiponectin (as well as other hormones) and upregulation of the renin-angiotensin axis and sympathetic nervous system activity. Many unanswered questions remain surrounding both the causes of obesity-related kidney disease and its optimal treatment.

Visceral Fat Is Linked to Inflammation in Dialysis Patients, While Subcutaneous Fat Marks Nutritional Status

In dialysis patients, visceral fat is a marker of inflammation while subcutaneous fat is a marker of nutritional status, suggests a study in *American Journal of Kidney Diseases*.

The cross-sectional study included 609 adult hemodialysis patients enrolled in the US Renal Data System's ACTIVE/ADIPOSE study. Participants underwent several measurements: body mass index (BMI), waist circumference as an indicator of visceral fat, and percentage body fat as an indicator of subcutaneous fat. The two fat measures were evaluated for association with markers of inflammation, nutrition, and adiposity-related hormones.

Body mass index was directly related to the inflammatory markers C-reactive protein and interleukin-6 (IL-6), but not with markers of nutrition, i.e., prealbumin or albumin. BMI was inversely associated with adiponectin and directly related to leptin. In a model including proxies for both visceral and subcutaneous fat, percentage body fat—the indicator for subcutaneous fat—was unrelated to C-reactive protein, but was inversely associated with IL-6.

Also in this model, waist circumference was associated with markers of inflammation but was inversely associated with prealbumin and albumin. Percentage body fat was directly related to these nutritional markers. Waist circumference was indirectly related to adiponectin and indirectly related to leptin.

Dialysis patients with BMI higher than the normal range generally have a higher survival rate, a phenomenon called the "obesity paradox," which has confounded researchers and practitioners. Yet BMI is a general marker of adiposity, and does not distinguish between subcutaneous and visceral fat, which may have differing metabolic and inflammatory characteristics. Determining the type of fat—visceral or subcutaneous—may help unravel the obesity paradox, but longitudinal studies are needed to clarify the associations between measures of body fat and markers of inflammation.

Added to previous findings, the results of this cohort study of dialysis patients suggest that "higher subcutaneous fat may account for the observed survival advantage associated with higher BMI."

Delgado C, et al. Associations of body mass index and body fat with markers of inflammation and nutrition among patients receiving hemodialysis. *Am J Kidney Dis* 2017; DOI: http://dx.doi.org/10.1053/j.ajkd.2017.06.028].

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