Progressive kidney disease may be predicted by proteins in urine

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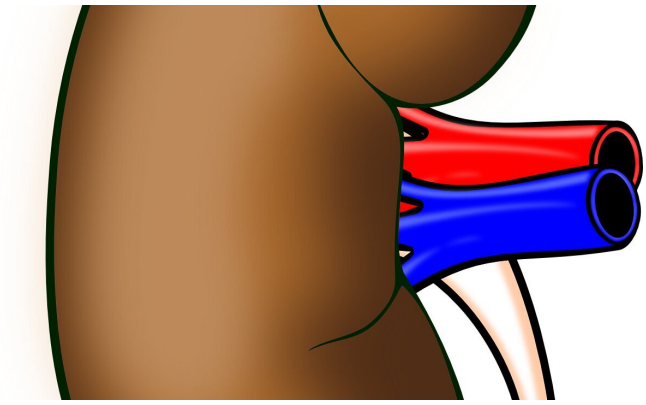

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In a study of people who were diagnosed during hospitalization with the short term but serious disorder called acute kidney injury (AKI), Johns Hopkins Medicine researchers showed that the levels of three proteins isolated from the urine of these patients could serve as biomarkers to predict the likelihood of progression to chronic kidney disease (CKD), kidney failure—also called end stage renal disease (ESRD)—or death.

The findings are reported in the Feb. 1, 2021, issue of *The Journal of Clinical Investigation*.

AKI, as described by the National Kidney Foundation, is a "sudden episode of kidney failure or kidney damage that happens within a few hours or a few days." It causes waste products to build up in the blood, making it hard for the kidneys to maintain the correct balance of fluids in the body.

Symptoms of AKI differ depending on the cause and may include: too little urine leaving the body; swelling in the legs and ankles, and around the eyes; fatigue; shortness of breath; confusion; nausea; chest pain; and in severe cases, seizures or coma. The disorder is most commonly seen in patients in the hospital whose kidneys are affected by medical and surgical stress and complications.

"Although many studies have investigated biomarkers to detect AKI in its early stages and forecast the short-term outcomes of the condition, little research has been devoted to examining biomarkers for their ability to predict long-term kidney function," says Chirag Parikh, Ph.D., director of the Division of Nephrology at the Johns Hopkins University School of Medicine and the study's senior author. "We looked at three proteins easily measured from urine—and known to be altered in response to kidney inflammation or damage—to see if they could be effective in making those predictions."

The three proteins evaluated were monocyte chemoattractant protein 1 (MCP-1), also known as C-C motif chemokine ligand 2 (CCL2); uromodulin (UMOD) and YKL-40, also known as chitinase 3-like 1 (CHI3L1). Their levels in urine were measured for each of 1,538 study participants—half of whom were diagnosed with AKI during their hospitalizations—at three months after release from the hospital. Following this baseline measurement, the patients were followed for an extended period of time (median: 4.3 years) to see how many progressed to CKD or ESRD. Throughout the monitoring period, the researchers assessed the relationship between the baseline biomarker levels for each patient with changes in estimated glomerular filtration rate (eGFR), a measure of kidney function (a low number indicates poor performance); the development of CKD or ESRD; or death from kidney failure.

The relationship between baseline biomarker levels and composite kidney outcome (development of CKD or ESRD) was defined using a statistical model that produces a hazard ratio—a measure over time of how often specific events (in this case, declining kidney performance) happen in a study group (the patients with AKI during their

hospitalizations) compared with their frequency in a control group (the patients without AKI during their hospitalizations). In this study, a hazard ratio of 1 suggests no difference between the groups, and a ratio greater than 1 indicates a greater likelihood of a poor composite kidney outcome. Likewise, a ratio less than 1 shows a decreased chance.

The researchers found that higher MCP-1 and YKL-40 levels in patients with AKI during hospitalization were associated with increased progression of the acute condition to CKD or ESRD. The hazard ratio for MCP-1 was 1.32 while the ratio for YKL-40 was 1.15. Both baseline protein measures also were associated with progressively declining eGFR during the observation period.

The opposite was observed for those whose baseline urine samples had higher UMOD levels, with a hazard ratio of 0.85 for CKD or ESRD development. Higher UMOD also predicted less chance of declining renal function over time.

To confirm their results, Parikh and his colleagues studied mice in which AKI was followed by either renal atrophy (shrinking of the kidney, which models progressive kidney decline) or repair. In the mice with atrophy, the researchers observed more activity by the genes that produce MCP-1 and YKL-40. In the repair mice, there was more production of UMOD. This, the researchers say, suggests that MCP-1 and YKL-40 may hinder the ability of kidneys to repair damage caused by AKI, setting the stage for progression to more serious kidney disease. On the other hand, they say UMOD production may enhance recovery.

"Based on our findings, the three proteins we studied show great promise as biomarkers for predicting the risk of CKD or ESRD following AKI, and with more research to prove their abilities, they may become valuable screening tools for physicians in the future," says Parikh.

More information: Jeremy Puthumana et al. Biomarkers of inflammation and repair in kidney disease progression, *Journal of Clinical Investigation* (2020). DOI: 10.1172/JCI139927