Study identifies new risk factor for heart disease among kidney dialysis patients

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Kidney failure affects 25 million individuals in the U.S. and many more throughout the world. Loss of kidney function means the majority of these patients must undergo dialysis treatments to remove excess fluids and waste products. Although dialysis therapy coupled with medication has improved the life expectancy for people with kidney failure, for unknown reasons, patients' risk of sudden heart failure and death remains 10 to 20 times greater than average.

Now, a study led by researchers at Beth Israel Deaconess Medical Center (BIDMC) and Massachusetts General Hospital helps explain why this may be the case. Appearing on-line today in *Science Translational Medicine*, the new findings show that a process known as protein carbamylation contributes to heart disease risk among patients with kidney failure undergoing dialysis, and demonstrates that a blood test to measure carbamylated albumin protein can help clinicians better gauge the effectiveness of dialysis and identify patients at risk of cardiac complications. The findings additionally suggest the need for further investigation to determine if therapy with supplemental amino acids could help to prevent the carbamylation process.

"Patients with kidney failure often accumulate urea in their blood because it is a chemical byproduct of metabolism normally eliminated in the urine or removed by dialysis treatments," explains first author Anders Berg, MD, PhD, a clinical chemist in the Department of Pathology at BIDMC and Instructor in Pathology at Harvard Medical School. Although urea is generally non-toxic, in some cases it can

degrade into cyanate, a toxic chemical that binds to and permanently modifies proteins through a process known as carbamylation.

"These modifications can make proteins inactive, or worse, can make them toxic," says Berg. "For example, when the cholesterol-carrying blood proteins LDL and HDL are carbamylated, instead of heading for tissues where they would normally be metabolized, they become attracted to atherosclerotic plaques which can lead to the development of atherosclerosis or hardening of the arteries."

Knowing that there is growing evidence that urea and protein carbamylation are important contributors to the risk of heart disease and death in patients with kidney failure, Berg and his collaborators hypothesized that measurements of carbamylated albumin – the most abundant protein in the blood —could provide an index of patients' blood urea concentrations and could be used in a blood test to provide clinicians with information on how well dialysis treatments are working to remove body waste products from patients with kidney failure.

As predicted, in two independent clinical experiments, the investigators demonstrated that increased carbamylated albumin is strongly associated with an elevated risk of premature death in patients on dialysis. They additionally found that increased carbamylated albumin in dialysis patients was linked with low blood concentrations of amino acids, the building blocks of proteins.

"This suggests that amino acid deficiencies may contribute to increased protein carbamylation in dialysis patients," says Berg. "In separate experiments in both cells and in mice, we found that amino acids act as carbamylation scavengers, competitively inhibiting protein carbamylation."

The researchers were able to generate their findings through a variety of

complex studies, including protein screening experiments to search for sites of carbamylation on albumin and observational studies in which they first measured albumin carbamylation in blood samples from patients with kidney disease and then followed the patients to determine whether the extent of carbamylation correlated with risk of premature death. The investigators also measured blood concentrations of amino acids in 187 patients to determine if amino acid deficiencies were linked with increased protein carbamylation. They also conducted experiments to test whether inducing amino acid deficiencies in animals led to increased protein carbamylation by urea. Finally, they conducted test tube experiments to investigate whether amino acids could directly inhibit protein carbamylation.

"Although dialysis therapy is life-saving and necessary to remove excess water and urea for patients with kidney failure, it also depletes patients' amino acids and other essential nutrients. In this way it removes both the good and the bad, and thus simply increasing patients' dialysis treatments will not necessarily reduce protein carbamylation," says Berg, adding that future studies will be needed to test whether amino-acid supplementation therapy reduces protein carbamylation and its associated risks, or if there are ways of modifying dialysis methods in order to remove urea without depleting amino acids.

"The mechanisms that lead to cardiovascular disease in patients with chronic kidney disease have remained elusive," says nephrologist Vikas Sukhatme, MD, PhD, Chief Academic Officer of BIDMC. "This paper provides an important first step in identifying kidney failure patients on dialysis at risk for cardiovascular disease and providing a rationale for treating them with inexpensive and non-toxic medicines such as amino acids."

Provided by Beth Israel Deaconess Medical Center