Editorial

Uromodulin, a novel biomarker for cardiovascular risk assessment?

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Uromodulin (Tamm-Horsfall protein) is a renal specific glycoprotein produced by the epithelial cells of the thick ascending limb of the loop of Henle. Several important roles have been identified for uromodulin including ion transportation, water maintenance, electrolyte balance and innate immunity of the urinary tract (1,2). In addition, urine uromodulin levels are an important marker for renal tubular function (3) and mutations in the uromodulin (*UMOD*) gene result in autosomal dominant tubulointerstitial kidney disease (ADTKD), medullary cystic kidney disease or uromodulin-associated kidney disease (4,5). The renal abnormalities caused by *UMOD* mutations are characterized by tubulointerstitial dysfunction from aggregation of abnormal uromodulin protein and manifested by defective urinary concentration, hyperuricemia and lower urinary uromodulin levels culminating in early onset end stage renal disease among affected individuals (4-7). In addition, *UMOD* gene variants are also associated with the development of chronic kidney disease (3) and hypertension in the general population (8).

The publication by Delgado *et al.* (9) is an important development in moving forward the paradigm of uromodulin as a biomarker and expanding its clinical implications to beyond renal pathophysiology. In the study, serum uromodulin levels were determined for more than 3,000 patients undergoing coronary angiography and participating in the Ludwigshafen Risk and Cardiovascular Health study. The association between serum uromodulin at baseline and all-cause as well as cardiovascular mortality was assessed by Cox regression analysis over a 10-year period. The results showed that patients with higher serum uromodulin were younger, and more likely to have lower blood pressure, triglycerides, hemoglobin A1C, high-sensitivity C-reactive protein (hsCRP), N-terminal pro-B-type natriuretic peptide (NT-proBNP) and high LDL levels. Serum uromodulin levels correlated positively with eGFR and inversely with serum creatinine levels. Higher serum uromodulin concentrations were found in patients without coronary artery disease, diabetes and hypertension. Higher quartiles of uromodulin were significantly associated with reduced all-cause mortality. The association between high uromodulin levels and decreased mortality remained significant after adjusting for age, sex, diabetes, body mass index, hypertension, smoking, eGFR as well as hsCRP, NT-proBNP and medications in a multivariate model. Serum uromodulin information when added to risk prediction models such as the European Society of Cardiology heart score and the Pooled Cohort Equation, improved the Harrell C statistics for all-cause mortality and cardiovascular death and lead to a net reclassification index for 9% of the population.

This study adds a new candidate to the list of renal specific biomarkers for predicting cardiovascular outcomes. Prior studies have demonstrated important role of serum creatinine (10), urinary albumin (11) and serum cystatin C levels (12,13) for predicting cardiovascular mortality among various populations. Although, Garimella *et al.* (14) have previously reported low urinary uromodulin levels to be associated with development of progressive renal disease and increased all-cause mortality in an elderly population.

However, there are significant difficulties with measuring urine uromodulin levels (15) and serum uromodulin measurement remains the preferred assay (15,16). This is the first study to assess and determine the predictive value of serum uromodulin for cardiovascular mortality in patients being evaluated for the presence of coronary artery disease. The major strengths of the study include a large sample size; prospective and robust study design and long term clinical follow up.

However, additional studies for confirmation of observed findings in diverse populations and elucidate the biological mechanisms are needed before serum uromodulin measurements can be applied in routine clinical setting. The study by Delgado *et al.* (9) is likely to stimulate further interest in uromodulin as a biomarker for both renal dysfunction as well as cardiovascular outcomes.

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Footnote

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