A Systems-Level View of Renal Metabolomics

Eugene P. Rhee, MD

Summary: The measurement of select circulating metabolites such as creatinine, glucose, and cholesterol are integral to clinical medicine, with implications for diagnosis, prognosis, and treatment. Metabolomics studies in nephrology research seek to build on this paradigm, with the goal to identify novel markers and causal participants in the pathogenesis of kidney disease and its complications. This article reviews three themes pertinent to this goal. Each is rooted in long-established principles of human physiology, with recent updates enabled by metabolomics and other tools. First, the kidney has a broad and heterogeneous impact on circulating metabolites, with progressive loss of kidney function resulting in a multitude of small molecule alterations. Second, an increasing number of circulating metabolites have been shown to possess functional roles, in some cases acting as ligands for specific G-protein–coupled receptors. Third, circulating metabolites traffic through varied, and sometimes complex, interorgan circuits. Taken together, these themes emphasize the importance of viewing renal metabolomics at the systems level, recognizing the diverse origins and physiologic effects of blood metabolites. However, how to synthesize these themes and how to establish clinical relevance remain uncertain and will require further investigation.
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The metabolome refers to the global collection of small molecules (eg, sugars, amino acids, organic acids, nucleotides, acylcarnitines, lipids, bile acids, and so forth) in a cell or biologic specimen.[1] This includes many molecules, such as creatinine, urea, uric acid, lactic acid, glucose, triglycerides, and cholesterol, which routinely are measured in clinical practice. A consideration of a few of these molecules is instructive. Creatinine is released primarily from muscle and is excreted by the kidney. Blood levels of creatinine are the most commonly used biomarker of renal failure, but the molecule itself is not harmful. Glucose has many sources, including diet, as well as gluconeogenesis within the liver and kidney. It is freely filtered at the glomerulus, but then undergoes almost complete tubular reabsorption such that its blood levels are not directly affected by renal failure.[2,3] It is both a fundamental fuel required throughout the body, but also deleterious if chronically increased. Cholesterol can be absorbed through diet or synthesized and released from the liver. It circulates in the context of lipoprotein particles and thus does not undergo glomerular filtration; as with glucose, prolonged increases are harmful. Altogether, these examples show several important features of circulating metabolites, including the heterogeneous impact of renal failure on blood levels, the potential for both salutary and adverse functional effects, and their complex interorgan traffic. As detailed in this article, each of these features or themes has been reinforced and expanded with the application of metabolomics across clinical, basic, and physiologic studies.

THE IMPACT OF KIDNEY FUNCTION ON THE METABOLOME

The kidneys generate approximately 140 L of glomerular filtrate per day, only to reabsorb the vast majority of filtered sodium and water, glucose, amino acids, and other urinary constituents. Although this continuous cycle of filtration and reabsorption seems energetically wasteful, it permits very high rates of clearance of freely soluble waste products such as creatinine and urea. In addition to glomerular filtration, normal renal excretory function includes tubular secretion, a critical mechanism for the excretion of protein-bound or lipophilic waste products that do not readily cross the glomerular filtration barrier. Finally, the kidneys also take up and catabolize some circulating small molecules, such as asymmetric dimethylarginine (ADMA) and S-adenosylhomocysteine (as well as numerous peptides).[4–6] Thus, through a combination of filtration, reabsorption, secretion, and metabolism, the kidneys have a broad and heterogeneous impact on circulating metabolite levels, minimizing the loss of desired nutrients while facilitating the excretion of unwanted metabolic waste products.

Metabolites that normally are cleared by the kidneys accumulate as kidney function declines. The relative increase of metabolites, however, varies significantly. For example protein-bound metabolites or metabolites

Nephrology and Endocrinology Divisions, Massachusetts General Hospital, Boston, MA.

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Address reprint requests to Eugene P. Rhee, MD, Thier Building, 1051, Massachusetts General Hospital, 50 Blossom St, Boston, MA 02114. E-mail: eprhee@partners.org,

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that are catabolized within the kidney can increase out of proportion to the increase in creatinine levels.[7] This discrepancy is magnified among patients with end-stage renal disease (ESRD) on dialysis. For both hemodialysis and peritoneal dialysis, the clearance of freely soluble metabolites such as creatinine is substantially below normal, but the clearance of protein-bound metabolites is even lower, because it is free (unbound) levels that determine the diffusion gradient across the hemodialysis or peritoneal membrane. For example, one study showed increases of phenylacetylglutamine (122-fold), hippurate (108-fold), indoxyl sulfate (116-fold), and p-cresol sulfate (41-fold), four metabolites normally cleared by tubular secretion, significantly greater than for urea (5-fold) and creatinine (13-fold) among ESRD patients.[8]

Building on these long-established principles of renal physiology, metabolomics studies have generated a broader and more detailed view of how kidney function impacts the metabolome. This includes relatively smaller studies of individuals across different stages of chronic kidney disease (CKD),[9–11] as well as large studies correlating metabolites with estimated glomerular filtration rate (eGFR) in population-based cohorts.[12] For example, Sekula et al[13] measured approximately 500 blood metabolites in 1,735 participants of the Cooperative Health Research in the region of Augsburg (KORA F4) study, followed by replication in 1,164 individuals in the TwinsUK registry. Most (≥95%) of the individuals across these studies had an eGFR greater than 60 mL/min/1.73 m^2. Despite a relative paucity of CKD in these samples, this "metabolome-wide association study" nevertheless showed the substantial impact of kidney function; in KORA F4, 112 metabolites were associated significantly with eGFR at a conservative Bonferroni adjusted significance threshold, 54 of which were replicated in TwinsUK.[13] For select metabolites most strongly correlated with eGFR, estimated on the basis of serum creatinine or cystatin C, the investigators then examined their association with measured GFR among 200 participants of the African American Study of Kidney Disease and Hypertension study, highlighting c-mannosyltryptophan and pseudouridine ($r = 0.78$ for both) as alternative or complementary markers of kidney function. One potential advantage of these markers is that unlike creatinine, their levels largely are unaffected by sex.

Measurement of peripheral blood levels can provide a catalog of metabolites that increase when kidney function is reduced, but it does not necessarily prove that the increases are because of reduced renal clearance. Concurrent measurement in urine can be helpful in this regard. For example, Duranton et al[14] measured amino acids and amino acid derivatives in plasma and urine from 52 individuals across different stages of CKD and plasma only from 25 individuals on dialysis. By examining paired plasma and urine, the investigators could conclude that uremic increases in plasma ADMA are caused by decreased urinary clearance, whereas increases in plasma citrulline are caused by systemic overproduction. Increased overproduction can result from changes in diet or changes in endogenous metabolism triggered by renal failure.

Direct measurement of metabolite gradients across the renal vasculature also is informative. We applied metabolomics to plasma obtained from the aorta and renal vein of nine individuals who already were scheduled for left and right heart catheterization.[15] Indications for cardiac catheterization spanned evaluation of valve disease, dyspnea, and monitoring of orthotopic heart transplants. Their mean age was 72.2 years, mean eGFR was 65.4 mL/min/1.73 m^2, and the prevalence of comorbidities such as coronary disease (66%), hypertension (100%), and type 2 diabetes (33%) was high. With these caveats, Figure 1 shows the distribution of the mean venous to arterial ratio for approximately 220 metabolites, providing a graphic depiction of how the human kidney impacts these circulating metabolites. Several observations warrant mention. First, many metabolite levels are lower in the renal vein than in the aorta, consistent with some degree of renal clearance (many of the metabolites that do not change or change minimally from aorta to renal vein are lipids). Second, the decrease in creatinine levels provides an index for the effect of glomerular filtration, acknowledging that the 16% decrease in creatinine in this sample is less than would occur in healthy adults. Third, a substantial number of metabolites decrease more than creatinine does from the aorta to renal vein, implicating some additional or alternative mechanism for their excretion, such as tubular secretion or intra-organ metabolism. Paired analysis of urine samples was performed to formally show tubular secretion of kynurenic acid (fractional excretion in urine >100%) and intra-organ metabolism of choline and citrulline (very low fractional

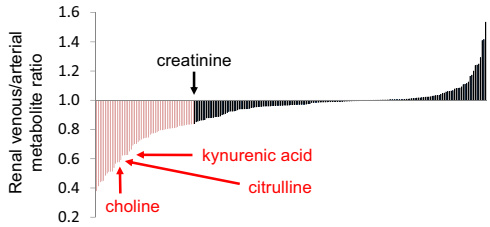

Figure 1. Renal arteriovenous metabolite gradients in human beings. Mean venous to arterial ratios ([V]/[A]) for approximately 220 metabolites, ordered left to right on the x-axis from the lowest to highest ratio, are provided. For any given metabolite, [V]/[A] < 1 is consistent with net renal uptake, whether via filtration, secretion, and/or metabolism, whereas [V]/[A] > 1 suggests net release by the kidney. Representative metabolites, including creatinine, kynurenic acid, choline, and citrulline, are highlighted.

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