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# Hypothesis: Potential Utility of Serum and Urine Uromodulin Measurement in Kidney Transplant Recipients?

Andrew G. Bostom, MD,<sup>1</sup> Dominik Steubl, MD,<sup>2</sup> and Allon N. Friedman, MD<sup>3</sup>

**Abstract:** Seventy years after its discovery, studies of the myriad properties, and potential disease associations of uromodulin are now burgeoning. Although normative ranges for serum/plasma uromodulin concentrations were established over 30 years ago, their external validation occurred only in very recent, larger studies. As tubular function indices, serum and urinary uromodulin may be more sensitive indicators of kidney graft dysfunction undetected by glomerular filtration markers, or proteinuria. Moreover, 2 sizable, just published longitudinal reports revealed that lower serum uromodulin levels were associated with cardiovascular disease (CVD) outcomes, total mortality, and infectious disease deaths, in patients with known or suspected coronary heart disease. Preliminary longitudinal studies have reported that reduced levels of plasma or serum uromodulin were linked to progression to end-stage renal disease in chronic kidney disease patients, and graft failure in kidney transplant recipients (KTRs). Conflicting data on the associations, or lack thereof, between lower urinary uromodulin concentrations and accelerated loss of renal function, or renal failure, in nontransplant chronic kidney disease patients, are perhaps due, in part, to analytical limitations in determining urine uromodulin. Potential longitudinal associations between serum and urinary uromodulin concentrations, and CVD outcomes, graft failure, and all-cause mortality, await validation in large, diverse cohorts of chronic KTRs. Taking advantage of an efficient case-cohort design scheme, we demonstrate how the completed FAVORIT clinical trial cohort might be ideally suited to evaluate these associations. Using available case-cohort sample data, statistical power simulations are provided to detect relative risk estimates of 1.50 for CVD (n = 309 events), 1.56 for graft failure (n = 223 events) or 1.50 for death from any cause (n = 320 events), comparing values below the median, to values equal to or above the median for serum uromodulin values. Edifying data such as these would advance our understanding of the hypothetical utility of uromodulin measurement in KTRs considerably.

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“The thing that hath been, it is that which shall be; and that which is done is that which shall be done: and there is no new thing under the sun.” [Ecclesiastes 1:9]<sup>1</sup>

In his gloss on this verse’s meaning, the great Biblical commentator of the Middle Ages, Shlomo Yitzchaki (“Rashi”; d. 1105), emphasized a seeming paradox. Rashi averred it meant that through ongoing meditation—study—one finds “new insights.”<sup>1</sup> Nearly 70 years after its first characterization as Tamm-Horsfall protein,<sup>2</sup> followed by “rediscovery”

as uromodulin, over 3 decades later,<sup>3</sup> studies of the apparent myriad properties, and potential disease associations of this 85 kDa glycoprotein,<sup>3</sup> are burgeoning.<sup>4,5</sup>

Cardiovascular disease (CVD) is the leading cause of mortality in kidney transplant recipients (KTRs), whereas renal graft loss remains a major morbidity.<sup>6-9</sup> Data from KTRs and nontransplant populations indicate both serum and urinary uromodulin, as tubular function indices, may be more sensitive indicators of kidney graft dysfunction not detected by glomerular filtration markers, or proteinuria, and that uromodulin could also have anti-infectious properties.<sup>10-20</sup> Lower serum uromodulin levels have, in addition, been associated prospectively with CVD outcomes, all-cause mortality,

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<sup>1</sup> Center For Primary Care and Prevention, Memorial Hospital of Rhode Island, Pawtucket, RI.

<sup>2</sup> Department of Nephrology, Klinikum rechts der Isar, Technische Universität München, Munich, Germany.

<sup>3</sup> Department of Medicine, Indiana University School of Medicine, Indianapolis, IN. The authors declare no funding or conflicts of interest.

All the authors contributed to the writing and editing of this focused review.

Correspondence: Andrew G. Bostom, MD, 130 Gold Mine Road, Chepachet, RI 02814. (abostom@cox.net).

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and infectious disease deaths, in patients with established or suspected coronary heart disease.<sup>21,22</sup> Preliminary longitudinal studies have further suggested that reduced levels of plasma or serum uromodulin were linked to progression to end-stage renal disease (ESRD) in chronic kidney disease (CKD) patients,<sup>23</sup> and graft failure in KTRs.<sup>24</sup> Although there are some significant contrary data, reduced urinary uromodulin concentrations have been associated with the development of accelerated loss of renal function, or renal failure, in nontransplant CKD patients, and the incidence of urinary tract infections in the elderly.<sup>25-33</sup>

### Uromodulin: Descriptive Studies and Their Consistency Across 3 Decades

Synthesized exclusively in the kidney, within the nephron's thick ascending limb (TAL), but also in the distal convoluted tubule of the nephron,<sup>4,5</sup> uromodulin is the most abundant protein constituent of normal urine,<sup>4,5</sup> which also reaches the systemic circulation via basolateral TAL production.<sup>5</sup> Normative ranges for serum/plasma uromodulin concentrations were established more than 3 decades ago by radioimmunoassay,<sup>10-12</sup> and validated in very recent, larger studies using ELISAs.<sup>5,15,17</sup> Two pioneering, seminal reports published in 1981<sup>10</sup> and 1985<sup>11</sup> by St. Bartholomew's Hospital (London) investigators, based on serum/plasma and urinary radioimmunoassay determination of uromodulin, revealed that the glycoprotein was a normal component of human serum, as well as urine, whose concentrations were intimately related to the volume of functioning renal mass. Specific findings,<sup>10,11</sup> which supported this concluding assessment, were as follows: undetectable uromodulin concentrations in anephric ESRD patients on maintenance hemodialysis, and among those with minimally functioning kidneys in situ, a significant negative correlation between serum uromodulin concentrations, and a surrogate for residual renal function, time (months) since initiation of hemodialysis<sup>10</sup>; a significant decline in pre-nephrectomy serum uromodulin levels on kidney donation by healthy donors free of renal disease; conversely, a marked elevation of serum uromodulin concentrations in ESRD patients after successful kidney transplantation<sup>10</sup>; statistically significant correlations between 24-hour urinary uromodulin excretion and plasma uromodulin concentrations in both persons with and without CKD<sup>11</sup>; and in patients with glomerulonephritis and available renal biopsy data, significantly higher urinary excretion of uromodulin per milliliter of creatinine clearance, among those with comparatively well-preserved tubules, relative to those with extensive tubular atrophy.<sup>11</sup>

### Uromodulin and Renal Function in KTRs and Nontransplant CKD

A 1985 study of 115 KTRs by Avis et al<sup>12</sup> provided confirmatory evidence for the possible utility of serum uromodulin in distinguishing what they dubbed "tubulotoxic effects." Their findings indicated that even when renal function (ie, glomerular filtration estimated as 1/serum creatinine) was comparable (unadjusted, and by analysis of covariance-adjustment) between 63 KTRs treated with the potentially tubulotoxic calcineurin inhibitor, cyclosporine A (CsA), 52 KTRs without calcineurin inhibitor, treated only with azathioprine/prednisolone, and 30 healthy controls free of CKD, the KTRs receiving CsA had disproportionately low

serum uromodulin concentrations.<sup>12</sup> Dawney et al<sup>13</sup> subsequently reported in 1988 that 10 patients with primary biliary cirrhosis on CsA therapy for a median of 26-months, had significantly lower serum and urinary uromodulin concentrations, compared to non-CsA using healthy controls, without CKD. The primary biliary cirrhosis patients, in addition, were better differentiated from the controls by serum uromodulin, relative to serum creatinine.<sup>13</sup> Lastly, McLaughlin et al<sup>14</sup> (in 1993) reported that among 31 KTRs undergoing allograft biopsy for presumptive acute rejection, those who experienced ischemic tubular damage (7 episodes of acute tubular necrosis), in the absence of histologic rejection, had significantly lower urinary uromodulin levels, compared to those with biopsy-proven rejection (37 episodes). Some 24 years later, a preliminary study of 91 kidney/kidney-pancreas transplant recipients just reported by Steubl et al<sup>24</sup> suggests that determining serum uromodulin concentrations could have longer term prognostic value. These investigators found that lower baseline serum uromodulin concentrations were independently associated with subsequent graft loss.<sup>24</sup> During a mean follow-up of  $3.6 \pm 2.2$  years there were 13 graft losses, with 9 of 13 of the failed grafts occurring among those with uromodulin concentrations in the lowest quartile.<sup>24</sup> A consistent longitudinal preliminary study of baseline plasma uromodulin concentrations, and ESRD development among 114 Chinese CKD patients surveilled for 5 years, was also just reported.<sup>23</sup> In this prospective analysis, the uppermost uromodulin quartile, relative to the first, was associated with a 55% lower risk of ESRD (hazard ratio [HR], 0.45; 95% confidence interval [CI], 0.33-0.71), after comprehensive multivariable adjustment for estimated glomerular filtration rate (eGFR), proteinuria, prevalent CHD, all major CVD risk factors, renin-angiotensin-aldosterone system inhibitor drug use, and serum phosphorus.<sup>23</sup>

### Conflicting Data From Studies of Urinary Uromodulin Concentrations

Studies of the potential associations between urinary uromodulin and clinical outcomes in CKD and non-CKD populations have yielded conflicting results,<sup>25-31</sup> perhaps due, in part, to analytical/methodologic limitations unique to urinary assays of the glycoprotein.<sup>5,32</sup> Youhanna et al<sup>32</sup> have demonstrated how storage conditions, centrifugation, vortexing, pH, electrolytes, and osmolality may adversely affect the stability of uromodulin in urine samples, potentially altering its polymerization, and causing conformational changes that modulate antigenic binding sites, and limit urinary assay reproducibility.<sup>5</sup> Scherberich et al,<sup>5</sup> in contrast, have reported finding only monomeric uromodulin, free of any aggregation processes, in serum. Moreover, serum uromodulin exhibited remarkable stability over weeks, even at increased temperatures.<sup>5</sup> Sejdiu and Torffvit<sup>28</sup> reported that the lowest quartile of urinary uromodulin concentrations was independently associated with a 3.8-fold increased risk for the development of stage 4 CKD, or ESRD requiring renal replacement therapy (31 events, pooled), as well as 2.9-fold greater all-cause (29 events), and 6.3-fold greater (12 events) CVD mortality risks, among  $n = 131$  type I diabetics followed up for a median of 14 years. However, these lower urinary uromodulin concentrations did not predict the development of stage 4 to 5 CKD (31 events), or overall mortality (58 events), in their parallel study group of 108 type II

diabetics surveilled for a median of 4.5 years.<sup>28</sup> A rather difficult to interpret study by Reznichenko et al<sup>29</sup> revealed that the middle tertile of urinary uromodulin excretion (mg/24 hours) was associated with a greater risk of death-censored graft failure (n = 42 events), relative to either the lowest or highest tertiles, after a median follow-up of 5.3 years among 600 chronic stable KTRs. As described by Zhou et al,<sup>25</sup> lower baseline urinary uromodulin levels (as a continuous variable, or below the median) were independently associated with more rapidly declining eGFR, and a greater extent of biopsy-determined tubular atrophy/interstitial fibrosis, in n = 185 patients with IgA nephropathy, during a 40 (±2)-month mean observation period. Contrastingly, in 2 nested case-control studies of populations without preexisting CKD, either lower urinary uromodulin was not associated with CKD incidence,<sup>30</sup> or elevated baseline urine concentrations of the glycoprotein appeared to predict the development of incident CKD.<sup>31</sup> The nested case-control study of CHD patients reported by Shlipak et al<sup>30</sup> found no difference in baseline urinary uromodulin levels between 100 cases whose eGFR declined to less than 60 mL/min (median, 44 mg/dL), versus the 94 controls with eGFRs remaining > 60 mL/min (median, 48 mg/dL). A prior case-control study by Köttgen et al,<sup>31</sup> from the population-based Framingham Study cohort revealed that among 100 incident CKD cases whose eGFR declined to less than 60 mL/min, relative to 100 matched controls with follow-up eGFRs greater than 60 mL/min, median urine uromodulin levels were 0.612 mg/dL, and 0.497 mg/dL, respectively. On the other hand, 2 large, independent reports of populations free of initial CKD by Garimella et al<sup>26</sup> from the elderly Cardiovascular Health Study (CHS) and Healthy Aging and Body Composition (Health ABC)<sup>27</sup> cohorts, respectively, each demonstrated that lower urinary uromodulin concentrations were associated with more rapid eGFR decline (n = 192 events in CHS; n = 91 events in Health ABC), and these associations were maintained upon adjustment for baseline eGFR, and urine albumin/creatinine ratio. Lower urine uromodulin concentrations were also associated with total mortality (n = 694 events) in CHS,<sup>26</sup> after adjustment for eGFR and urinary albumin/creatinine, but this relationship did not persist in Health ABC (n = 248 events) when adjusted for these kidney measures.<sup>27</sup> In summary, currently available published data on urinary uromodulin concentrations as a functional assessment of renal tubular function, and a predictor of adverse clinical sequelae, are rather equivocal.<sup>11,14,16,25-31</sup>

### Serum Concentrations of Uromodulin as a Predictor of Clinical Outcomes

The consistent detection of serum uromodulin (as Tamm-Horsfall protein) was reported already in 1981,<sup>10</sup> and normal serum/plasma ranges established by 1985.<sup>11,12</sup> Despite these developments over 3 decades ago, it is only a recent series of published reports which have reinvigorated study of circulating serum/plasma uromodulin concentrations as a marker of renal tubular function,<sup>5,15,17</sup> that may also predict the development of CVD outcomes,<sup>21,22</sup> ESRD,<sup>23</sup> and possibly, graft failure among KTRs.<sup>24</sup> Two prospective studies have evaluated the association between serum uromodulin concentrations and the risk of CVD outcomes and all-cause mortality in patients undergoing diagnostic coronary angiography.<sup>21,22</sup> Leisher et al<sup>21</sup> studied 529 patients

assessed for known or presumed CHD, and followed for a mean of 6.5 ± 1.8 years. The lowest tertile of serum uromodulin, relative to tertiles 2 and 3, pooled, was associated with a 2.15-fold (HR, 2.15; 95% CI, 1.43-3.22) increased risk for total mortality (95 events), and a 1.76-fold (HR, 1.76; 95% CI, 1.17-2.67) greater risk for the composite endpoint of CVD deaths, myocardial infarctions, and strokes (101 events), and these associations persisted after adjustment for major CVD risk factors and eGFR.<sup>21</sup> Delgado et al<sup>22</sup> reported concordant findings from a much larger cohort of patients, n = 3037, who underwent coronary angiography. During a median observation period of 9.9 years, there were 818 deaths, including 513 CVD deaths. Relative to the first (referent) quartile of serum uromodulin concentrations, the fourth quartile was associated with significantly lower risks for all-cause (HR, 0.57; 95% CI, 0.45-0.73) and CVD mortality (HR, 0.48; 95% CI, 0.35-0.66), on multivariable adjustment for age, sex, uromodulin genotype rs12917707, body mass index, diabetes, hypertension, smoking, eGFR, high sensitivity c reactive protein, N terminal pro b type natriuretic peptide, and lipid-lowering and antihypertensive/anti-ischemic drugs.<sup>22</sup> Consistent with its putative anti-infectious properties,<sup>4,19,20</sup> and the report by Garimella et al<sup>33</sup> that higher urinary uromodulin levels were associated with a lower incidence of urinary tract infections in an elderly, community-dwelling cohort, Delgado et al<sup>22</sup> also found that the upper quartile of serum uromodulin concentrations was associated with a reduced risk (HR, 0.27; 95% CI, 0.12-0.61) for fatal infections (66 events), after age, sex, and rs12917707 genotype adjustment. Lastly, serum uromodulin concentration shows promise as a diagnostic marker for the group of autosomal dominant heritable diseases caused by mutations in uromodulin coding (UMOD), dubbed Autosomal Dominant Tubulointerstitial Kidney Disease (ADTKD-UMOD).<sup>18,34</sup> These pathogenic mutations typically cause misfolded uromodulin accumulation within the endoplasmic reticulum of TAL renal tubular cells, resulting in CKD, and its progression to ESRD.<sup>18,34</sup> Satanovskij et al<sup>18</sup> have just reported that serum uromodulin concentrations were lower in all affected patients with a novel missense mutation in the UMOD gene (457 T > G; Cys153Gly), relative to all patients of the reference eGFR-matched CKD groups, and healthy, unaffected family members. These findings are consistent with the view that while serum uromodulin concentrations are strongly associated with functional renal (especially tubular) mass, the impact of UMOD variants, per se, on overall CKD risk, in addition to being age-dependent, is comparatively small.<sup>34</sup>

### Uromodulin Quantification in KTRs: Future Directions

Uromodulin/Tamm-Horsfall protein knockout mice are prone to excess calcium oxalate crystal formation, and the development of both renal papillary calcification, and ureteral stones, emphasizing another plausible role for the glycoprotein: inhibition of renal/urinary calcification processes.<sup>4,35</sup> Furthermore, recurrent human nephrolithiasis is associated with a greater extent of coronary artery calcification,<sup>36</sup> and it is well established that more pronounced vascular calcification occurs in diabetic KTRs.<sup>37</sup> The dynamic measure of serum calcification processes, “T50”/serum calcification propensity, has been associated, in cross-section, with diabetes, among KTRs.<sup>38,39</sup> Given the reported association

between reduced serum uromodulin concentrations and incident diabetes, or hyperglycemia,<sup>40</sup> the potential relationship between serum uromodulin, and “T50”/serum calcification propensity,<sup>38,39</sup> merits examination in KTR populations. Initial evidence that increased serum T50 (ie, more prolonged, meaning less prone to calcification) is associated with lower rates of mortality and graft failure in KTRs,<sup>38,39</sup> underscores the need to examine these possible interrelationships.

An early 2017 report by Hsu et al,<sup>41</sup> detailed how promising tubular injury biomarkers did not improve prediction of CKD progression (ie, incident ESRD, or a 50% reduction in eGFR, pooled; n = 581 events), relative to the combination of baseline eGFR and urinary albumin/creatinine ratio, among n = 2466 participants in the Chronic Renal Insufficiency Cohort Study. These sobering findings must be born in mind notwithstanding the small, preliminary studies discussed previously reporting “independent associations” between lower serum uromodulin concentrations and nontransplant CKD progression to ESRD,<sup>23</sup> or the occurrence of KTR graft failure.<sup>24</sup>

Data are required from large, well-characterized, multicenter KTR cohorts assessing the potential relationships between serum/plasma, or urinary uromodulin concentrations, and the development of graft failure, as well as CVD outcomes, and all-cause mortality, among chronic, stable KTRs. For example, taking advantage of a powerful, efficient case-cohort design scheme previously used,<sup>42,43</sup> the completed FAVORIT clinical trial<sup>44</sup> cohort might be ideally suited to evaluate these associations. One of us (A.B.), after establishing the availability of the relevant case-cohort sample data (ie, baseline serum and urine specimens, as well as germane nonmissing covariables) constructed Table 1 to gauge statistical power. Eighty percent power is estimated (see Table 1) at a 2-tailed alpha of 0.05 to detect relative risk estimates (RREs) of 1.50 (for CVD), 1.56 (for graft failure) or 1.50 (for death from any cause), comparing values below the median, to values equal to or above the median for serum uromodulin and serum T50, and values at or above the median to those below the median, for the serum glycemia indices, fructosamine, and glycated albumin. Adjusting the alpha value for 5-comparison increases, the RREs detectable with 80% power to 1.62 (for CVD), 1.72 (for graft failure), or 1.62 (for death from any cause). With the loss of only a few events,

the urine uromodulin RREs are almost identical. Edifying data such as these would advance our understanding of the hypothetical utility of serum and uromodulin measurement in KTRs considerably.

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**TABLE 1.**

**Power calculations for RREs for a potential FAVORIT trial case-cohort study based on dichotomizations of < vs ≥ the median for serum uromodulin and urine uromodulin, and serum T50; or ≥ vs. < the median for serum fructosamine and glycated albumin**

Outcome matrix	RREs detectable with 80% power	
	0.05, 2-sided α	0.05/5, corrected for 5 comparisons, 2-sided α
CVD <sup>a</sup> (309 events/908 KTRs)	1.50	1.62
CVD <sup>b</sup> (307 events/896 KTRs)	1.50	1.62
Graft failure <sup>a</sup> (223 events/908 KTRs)	1.56	1.72
Graft failure <sup>b</sup> (222 events/896 KTRs)	1.58	1.74
All-cause death <sup>a</sup> (320 events/908 KTRs)	1.50	1.62
All-cause death <sup>b</sup> (315 events/896 KTRs)	1.49	1.61

<sup>a</sup> Serum.

<sup>b</sup> Urine.

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