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Urine testing to differentiate glomerular from tubulointerstitial diseases on kidney biopsy

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A B S T R A C T

Background: Differentiating between glomerular and tubulointerstitial diseases can guide selection of appropriate patients for kidney biopsy. The aim of this study is to identify urine tests that can differentiate between these histological diagnoses.
Methods: In this sub-study of a prospectively enrolled cohort of participants with urine samples concurrent with their kidney biopsy, we tested the association of 24 features on urinalysis, urine sediment microscopy, and biomarkers of glomerular and tubular injury and inflammation with histological diagnosis of glomerular or tubulointerstitial disease. We selected a combination of features associated with glomerular disease using stepwise forward and backward regression, and LASSO algorithm after dividing the cohort into training (70%) and test (30%) sets.
Results: Of 359 participants, 121 had glomerular, 89 had tubulointerstitial diseases, and 149 were classified as mixed. Compared to patients with tubulointerstitial diseases, those with glomerular diseases had more dipstick hematuria (3+ vs. 1+, $P < 0.001$) and urine albumin (1.25 vs. 0.09 mg/mg, $P < 0.001$). Patients with glomerular diseases had higher levels of tubular health biomarkers (Uromodulin, 1.22 vs. 0.92, $P = 0.03$). In a multivariable model, higher urine albumin, dipstick blood, and urine uromodulin were independently associated with higher odds of glomerular diseases (test set AUC, 0.81 (0.69, 0.93)).
Conclusion: Urine tests, including urine albumin, dipstick blood, and urine uromodulin, were associated with the histological diagnosis of glomerular disease. These findings can help clinicians differentiate between glomerular and tubulointerstitial diseases and guide clinical decisions regarding a kidney biopsy.

1. Introduction

Histological examination of kidney biopsy tissue can help differentiate between glomerular and tubulointerstitial diseases, as well as differentiate between their underlying etiologies and subtypes. Primary glomerular diseases require an urgent kidney biopsy to guide targeted immunosuppressive therapy, whereas one common cause of tubular disease, acute tubular injury (ATI), is generally managed without a biopsy, and the other common cause, acute interstitial nephritis (AIN), is managed initially by discontinuing the offending drug followed by biopsy if there is no improvement in kidney function [1]. Since the kidney biopsy procedure carries risks [2–6], it is important to differentiate between these broad subtypes of kidney diseases before a biopsy and to select patients in whom the information obtained through a biopsy is likely to impact therapy decisions.

Several clinical and research urine tests are available to differentiate between glomerular and tubulointerstitial diseases. Clinically

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available tests include urinalysis, urine sediment microscopy, and urine albumin [7,8], which can indicate glomerular damage via features such as urinary presence of isomorphic or dysmorphic red blood cells (RBC) and casts, or presence of proteinuria or albuminuria. These clinical tests can also indicate presence of tubular damage through features such as renal tubular epithelial (RTE) cells or casts, or granular casts. In the research setting, laboratory tests such as neutrophil gelatinase-associated lipocalin (NGAL), interleukin-18, and kidney injury molecule (KIM)-1 can not only indicate presence of ATI but also specific sites of injury within the renal tubule [9]. Urine tests indicating tubulointerstitial inflammation such as tumor necrosis factor (TNF)-α and interleukin-9 can help diagnose the other common form of tubulointerstitial diseases, acute interstitial nephritis (AIN) [10–12]. Despite the availability of these tests, studies have generally evaluated these in isolation, in a small number of patients, or lacked histological confirmation of the diagnosis.

Here we evaluated a number of urine tests including urinalysis and urine sediment microscopy, as well as urine biomarkers of glomerular damage (albumin), ATI (NGAL, KIM-1, IL-18, MCP-1), and AIN (TNF-α and IL-9) for differentiating between biopsy-proven glomerular and tubulointerstitial diseases with the goal of identifying an optimal combination of urine tests that can differentiate between these diagnoses before a biopsy. We used samples and data from participants enrolled in a cohort with urine samples collected concurrent with a clinical kidney biopsy [10]. We hypothesized that markers of glomerular and tubular injury and inflammation may be used to differentiate glomerular from tubulointerstitial disease.

2. Materials and methods

2.1. Participants and settings

This is a sub-study of the Yale biopsy study and details of this cohort have been previously published [10,11,13]. Briefly, we enrolled patients scheduled to undergo a clinically indicated kidney biopsy at two Yale-affiliated hospitals from January 2015 to June 2018. We excluded kidney transplant recipients, patients who did not undergo a biopsy and patients who underwent a biopsy but could not receive a histological diagnosis due to insufficient material. We also excluded patients who did not have an available urine sample. This study was approved by the Yale Institutional Review Board (HIC number 11110009286) and all participants provided written informed consent.

2.2. Outcome: Glomerular, tubulointerstitial or mixed disease

Drawing from official biopsy reports, we classified the 15 most common diagnoses into three categories (Table S1): glomerular disease, tubulointerstitial disease, and mixed. Glomerular diseases included anti-Neutrophilic cytoplasmic autoantibody (ANCA), vasculitis, IgA nephropathy (IGA), post-infection glomerulonephritis (PIGN), amyloidosis, membrane proliferative glomerulonephritis (MPGN), minimal change disease (MCD), membrane nephropathy (MN), focal segmental glomerulosclerosis (FSGS), and lupus nephritis. Tubulointerstitial diseases included acute interstitial nephritis (AIN), contrast-induced nephropathy (CIN), and acute tubular necrosis (ATN). Arterionephrosclerosis, diabetic kidney disease (DKD), and any other diagnosis that did not fit into either a glomerular or tubulointerstitial disease classification were classified under mixed. We only reviewed the first diagnosis listed on histological report.

2.3. Exposure: urine dipstick, microscopy, and biomarkers

Urine samples were collected during the outpatient biopsy procedure visit or during inpatient hospitalization. We performed urine dipstick analysis using Clinitek Status analyzer (Siemens Healthcare Diagnostics Inc., Tarrytown, NY) which reported specific gravity, pH, protein, ketone, blood, and leukocyte levels on an ordinal scale. We also performed urine sediment microscopy (Laxco LMC4BF, Fisher Scientific) and took representative pictures at 10x and 40× magnification, which were analyzed and reported by a trained nephrologist (DGM) on an ordinal scale including RBCs, RBC casts, dysmorphic RBCs, WBCs, WBC casts, RTE cells, RTE casts, and granular casts. Urine samples were collected at a median (IQR) of 2.1 (−2.2, 4.0) before the biopsy and stored at −80 °C prior to biomarker analysis. After a single controlled thaw, we measured urine albumin and creatinine measurements using Randox RX Daytona machine and the other urine biomarkers using manufacturer-validated panels using the Mesoscale Discovery platform. We normalized urine albumin and other biomarkers to urine creatinine to account for urine concentration differences. The personnel performing urine dipstick, urine sediment microscopy and measuring biomarkers were blinded to the case status. A complete list of all tests evaluated in this study are presented in Table S2.

3. Data sources

3.1. Statistical analysis

We present all data as median (interquartile range) or count (percentage). We performed a Kruskal-Wallis or rank sum test and χ^2 test to compare urinalysis characteristics and biomarker levels between diagnoses of glomerular, tubulointerstitial, or mixed diseases. To select features associated with diagnosis of glomerular disease on histology, we used three feature selection methods: forward and backward stepwise regression with threshold P-value of 0.05, and a LASSO algorithm. For stepwise forward selection, we evaluated features sequentially in descending order of their univariable AUC for glomerular disease diagnosis. For this analysis, we divided our

dataset into temporal training (70%) and test (30%) sets. We performed feature selection only in the training set. We further evaluated features selected in all three methods by fitting a logistic regression model for outcome of glomerular disease in training set. We then applied model weights derived from the training set to the test set and reported area under receiver operating characteristics curve (AUC) in both training and test sets. In an alternate model, we included only clinically-available tests. For feature selection methods and multivariable models, we only included patients whose diagnoses were either clearly glomerular or tubulointerstitial diseases and excluded the patients whose diagnoses were classified as mixed. All analyses were conducted in STATA version 14.2 and significance was set at a level of 0.05.

4. Results

4.1. Cohort characteristics

Of the 392 eligible participants enrolled in the Yale Biopsy study, 359 participants were included in the final analysis (Fig. S1). Of the final 359 participants, 121 (34%) had a histological diagnosis of glomerular disease, 89 (25%) had tubulointerstitial disease, and 149 (42%) had mixed glomerular and tubulointerstitial disease. Patients with glomerular diseases tended to be younger than those with tubulointerstitial diseases (56 (43, 66) vs. 58 (39, 67), P = 0.008), while AKI was more common in patients with tubulointerstitial diseases than glomerular diseases (64% vs 58%, P = 0.02). Patients with tubulointerstitial diseases also tended to have higher urine output (775 (400, 1125) vs. 1400 (400, 1775), P = 0.03) (Table 1).

4.2. Urine tests between glomerular and tubulointerstitial diseases

Patients with glomerular diseases presented with more blood on urinalysis (3+ vs. 1+, P < 0.001), more dysmorphic red blood cells (RBCs) (32% vs. 10%, P < 0.001) on microscopy, and higher urine albumin to creatinine ratio (1.25 (0.49, 3.19) vs. 0.09 (0.03, 0.42) mg/mg, P < 0.001) than patients with tubulointerstitial diseases. Patients with glomerular diseases also had fewer renal tubular epithelial cell casts (2% vs. 12%, P = 0.001) and lower levels of ATI biomarker, NGAL, (95 (22, 494) vs. 200 (56, 773) ng/g, P = 0.01) than those with tubulointerstitial diseases (Table 2). We also noted that a urine biomarker diagnostic for AIN, TNF-α, was significantly lower (0.22 (0.09, 0.75) vs. 0.42 (0.15, 2.38) ng/g, P < 0.001) whereas a biomarker of tubular health, uromodulin, was significantly higher in glomerular diseases than tubulointerstitial diseases. We noted that urine NGAL, TNF-α and uromodulin were significantly different between glomerular disease and AIN but not between glomerular disease and ATI (Fig. 1).

4.3. Associations of urine tests with glomerular disease

In a receiver operating characteristic (ROC) analysis, we noted that urine albumin, dipstick RBCs and specific gravity, and urine TNF-α to creatinine had the highest area under ROC curve (AUC) for the outcome of glomerular disease (Table S3). Urine albumin, dipstick blood, and urine uromodulin to creatinine ratio were selected in all three feature selection methods (Table S4). In a multivariable logistic model consisting of these three features, higher dipstick blood, urine albumin to creatinine ratio, and urine uromodulin were associated with higher odds of glomerular disease. This model showed an AUC of 0.81 (0.69, 0.93) in the test set (Table 3). In an alternate model consisting only of variables widely available for clinical use urine albumin and dipstick blood, we noted an AUC

Table 1
Baseline characteristics.

Characteristic	Glomerular	Tubulointerstitial	Mixed	P-value
	121	89	149	
Demographics				
Age, years	56 (43, 66)	58 (39, 67)	60 (51, 67)	0.03
Female	59 (49%)	33 (37%)	68 (46%)	0.23
Black	21 (18%)	24 (27%)	43 (29%)	0.08
Body mass index, kg/m2	29 (25, 35)	28 (24, 32)	29 (25, 33)	0.34
Diabetes	18 (15%)	21 (24%)	87 (59%)	<0.001
Hypertension	81 (67%)	55 (62%)	125 (84%)	<0.001
Cirrhosis	13 (11%)	6 (7%)	7 (5%)	0.16
Chronic kidney disease	56 (52%)	48 (59%)	119 (84%)	<0.001
Baseline Laboratory Features				
Serum creatinine, mg/dl	1.2 (0.9, 1.7)	1.2 (0.9, 2.1)	1.7 (1.3, 2.4)	<0.001
Glomerular filtration rate, ml/min	58 (37, 84)	51 (31, 76)	35 (24, 47)	<0.001
Urine protein to creatinine ratio, mg/mg	2.2 (1.0, 5.0)	0.6 (0.2, 2.3)	1.9 (0.6, 5.1)	<0.001
Features at Biopsy				
Acute kidney injury	40 (58%)	53 (64%)	52 (44%)	0.02
Dialysis	4 (3%)	5 (6%)	8 (5%)	0.65
Hospitalized	54 (45%)	61 (69%)	64 (43%)	<0.001
Serum creatinine, mg/dl	2.0 (1.4, 3.7)	4.0 (2.4, 6.3)	3.2 (2.2, 5.0)	<0.001
Blood urea nitrogen, mg/dl	31 (21, 54)	36 (26, 58)	43 (32, 62)	<0.001

Kruskal Wallis or Chi2 test comparing all three groups; median (interquartile ranges) or count (percentage) shown.

Table 2
Comparison of urine tests between glomerular and tubulointerstitial disease.

Characteristic	Glomerular	Tubulointerstitial	Mixed	P-value [1]	P-value [2]
Dipstick					
Dipstick performed	121 (95%)	89 (97%)	148 (93%)		
Specific gravity	1.020 (1.015, 1.025)	1.015 (1.010, 1.020)	1.020 (1.015, 1.020)	<0.001	<0.001
pH	6.0 (5.5, 6.5)	6.0 (5.5, 6.5)	6.0 (5.5, 6.5)	0.66	0.80
Protein	3 (2, 3)	1 (0, 2)	3 (1, 3)	<0.001	<0.001
Ketone	10 (8%)	12 (13%)	10 (7%)	0.20	0.22
Blood*	3 (1, 4)	1 (1, 3)	2 (1, 3)	<0.001	<0.001
Leukocyte	0 (0, 0)	0 (0, 1)	0 (0, 1)	0.02	0.007
Urine Microscopy					
Microscopy performed	122 (96%)	85 (92%)	149 (93%)		
RBC cast*	19 (17%)	5 (7%)	13 (10%)	0.08	0.06
Dysmorphic RBC*	35 (32%)	7 (10%)	21 (16%)	<0.001	<0.001
RBC cell*	85 (78%)	46 (68%)	100 (76%)	0.27	0.13
WBC cast	4 (3%)	2 (2%)	2 (1%)	0.57	0.69
WBC cell	12 (10%)	19 (22%)	24 (16%)	0.05	0.01
RTE cell	30 (25%)	35 (41%)	44 (30%)	0.04	0.01
RTE cast	3 (2%)	10 (12%)	3 (2%)	0.001	0.007
Granular cast	45 (37%)	42 (49%)	53 (36%)	0.09	0.08
Urine biomarkers					
Glomerular disease					
Albumin	1.25 (0.49, 3.19)	0.09 (0.03, 0.42)	0.94 (0.11, 2.54)	<0.001	<0.001
Tubular injury and health					
IL-18	104.4 (50.6, 217.9)	75.1 (32.7, 184.1)	84.7 (40.9, 202.4)	0.07	0.03
KIM-1	4387 (2042, 10203)	3532 (1827, 6792)	3197 (1644, 6230)	0.03	0.12
MCP-1	1407 (586, 3939)	1799 (787, 4652)	1433 (517, 2991)	0.15	0.21
YKL-40	3593 (937, 14265)	6086 (1351, 21951)	9905 (1226, 75259)	0.04	0.13
NGAL	96 (22, 494)	200 (56, 773)	220 (52, 804)	0.02	0.01
Uromodulin	1.41 (0.84, 2.24)	1.13 (0.72, 1.78)	0.97 (0.58, 1.76)	<0.001	0.03
Interstitial Nephritis					
Interleukin-9	0.29 (0.14, 0.70)	0.36 (0.13, 1.45)	0.47 (0.20, 1.37)	0.04	0.46
TNF-α	0.22 (0.09, 0.75)	0.42 (0.15, 2.38)	0.39 (0.13, 2.64)	<0.001	<0.001

Kruskal-Wallis or rank sum and chi-square test performed; P-value [1] compares all three groups; p-value [2] compares glomerular vs. tubular; *excludes those with bladder catheters (n = 47); urine microscopy available in 359; urine biomarker values represent urine biomarker to urine creatinine ratio; all biomarkers are pg per mg of urine creatinine except albumin (mg/mg) and uromodulin (microg/mg). Data presented as count (percentage) or median (interquartile range).

of 0.79 (0.66, 0.91) in the test set (Table S5).

5. Discussion

In a cohort of participants prospectively enrolled at the time of their kidney biopsy, we analyzed the association of multiple characteristics noted on urinalysis, microscopy, and urine biomarkers with the histological diagnoses of glomerular or tubulointerstitial disease. We found that combining biomarkers of glomerular damage (urine albumin and dipstick blood) with a biomarker of tubular health, uromodulin, demonstrated a high AUC for differentiating glomerular from tubulointerstitial disease on kidney biopsy.

Previous studies have demonstrated the application of urine microscopy, urine sedimentation analysis, and biomarker tests for diagnosing various kidney diseases. Urine microscopy and urine sedimentation analysis were found to be more specific and cost-efficient [7,14], while biomarker tests were found to be more standardized and easier to measure in large numbers of patients [15]. One prior study specifically evaluated association of clinically-available urine tests with presence of glomerular disease on histology. In this study, the authors noted that presence of RBCs and protein on urinalysis showed a high specificity but low sensitivity for diagnosis of glomerular disease on biopsy [16]. This study also showed similar results for presence of dysmorphic RBCs on urine microscopy noting a sensitivity of 20% and specificity of 96% for biopsy diagnosis of glomerular disease.

Similar to this study, we noted that presence of urine albumin, dipstick blood, and dysmorphic RBCs were associated with presence of glomerular disease on biopsy. In addition, we evaluated levels of novel urine biomarkers of specific subtypes of tubulointerstitial diseases, namely ATI and AIN. We noted that biomarkers of ATI such as NGAL and of AIN such as TNF-α were lower in those with glomerular diseases than tubulointerstitial diseases, whereas a biomarker of tubular health, uromodulin, was higher in those with glomerular disease. We also used several feature selection methods to determine the optimal combination of various features for pre-biopsy diagnosis of glomerular disease. Elevations in biomarkers of damage to glomeruli (urine albumin and dipstick blood) and tubular health (uromodulin) were consistently associated with glomerular disease on biopsy. A model consisting of these three biomarkers showed a high AUC for glomerular disease diagnosis in the test set.

Our findings demonstrate the utility of urine biomarkers for differentiating between glomerular and tubulointerstitial diseases. These results mean that biomarkers of glomerular and tubular injury and health can be used to differentiate between those with glomerular and tubulointerstitial damage before a biopsy; biopsies can be expedited for those predicted to have glomerular disease,

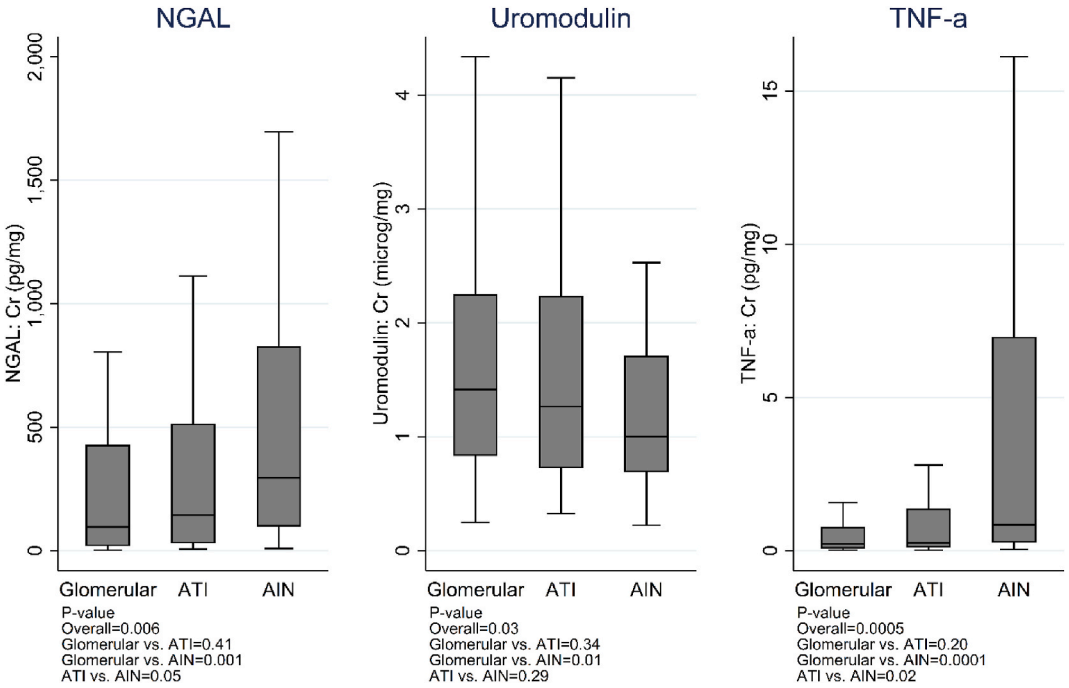

Fig. 1. Comparison of urine biomarkers between glomerular disease and subtypes of tubulointerstitial diseases.
ATI, acute tubular injury; AIN, acute interstitial nephritis; NGAL, neutrophil gelatinase associated lipocalin; TNF, tumor necrosis factor; Cr, creatinine; urine biomarker to urine creatinine ratios shown; horizontal line represents median, box represents 25th and 75th percentile; whiskers represent 5th and 95th percentile. Kruskal-Wallis test.

Table 3
Univariable and multivariable association of urine tests with histologically diagnosed glomerular disease on kidney biopsy.

Variables	Model 1	Model 2	Model 3	Model 4
	Odds ratio (95% confidence intervals)			
Albumin to creatinine ratio	1.73 (1.45, 2.07)	n/a	n/a	1.70 (1.40, 2.07)
Dipstick hematuria	n/a	2.06 (1.50, 2.81)	n/a	1.76 (1.21, 2.56)
Uromodulin to creatinine ratio	n/a	n/a	1.38 (1.02, 1.89)	1.68 (1.13, 2.49)
AUC, test set	0.77 (0.63, 0.91)	0.66 (0.52, 0.79)	0.54 (0.39, 0.69)	0.81 (0.69, 0.93)

Hematuria assumed to be absent when bladder catheter was present; per doubling in albumin; and TNF-α to creatinine ratio; TNF, tumor necrosis factor.

avoided for those thought to have ATI, and delayed while discontinuing culprit medications in those with AIN. However, more research must be conducted in the future to understand exactly how to differentiate between the various etiologies of glomerular and tubulointerstitial diseases through a combination of urinalysis, microscopy, and biomarker characteristics.

Strengths of our study include prospective patient enrollment allowing for consistent and standardized data collection, blinding of researchers performing the urine tests to the biopsy diagnosis, and multivariable analysis to determine the independent association of each feature. There were also some limitations. Only patients with a clinically indicated kidney biopsy at two Yale-affiliated hospitals were enrolled into this study, which may not be representative of all patients affected by glomerular and tubulointerstitial diseases. In addition, only the first diagnosis of the biopsy report was accepted as the official diagnosis. Finally, the study does not offer a definitive way to differentiate between various subtypes and specific etiologies of glomerular or tubulointerstitial diseases.

In conclusion, we demonstrate that a combination of biomarkers of glomerular damage such as urine albumin and dipstick blood and biomarkers of either of the two common forms of tubulointerstitial diseases (AIN or ATI) showed a high AUC for differentiating between patients with glomerular and tubulointerstitial disease. Future research could focus on using additional biomarkers to further characterize subtypes of glomerular and tubulointerstitial diseases.

Author statement

Conceptualization: ACT, DGM.
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Formal analysis: DGM.
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Supervision: DGM, CRP.
Validation: DGM.
Visualization: DGM.
Roles/Writing - original draft: ACT, DGM.
Writing - review & editing: all authors.

Declaration of competing interest

DGM and CRP are co-inventors of the pending patent application "Methods and Systems for Diagnosis of Acute Interstitial Nephritis" that is subject to an option for a license agreement with Renalytix AI Inc.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.plabm.2022.e00271.

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