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Recent Patents on Biomarkers **2015**, *5*, 35-43

A Biomarker Cluster for Polycystic Kidney Disease: Correlation with Cystic Index

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Abstract: Polycystic kidney disease (PKD) is characterized by the formation and expansion of fluid-filled cysts within the kidneys, painful renal enlargement and declining kidney function. Often, PKD manifests in other organs, including the liver and pancreas. In addition to cyst formation, interstitial collagen deposition is sometimes observed in both the kidney and the liver. While a diagnosis of PKD may be made using ultrasonography coupled with family history, monitoring disease progression is challenging as imaging techniques remain inadequate to track an increasing cystic index over time. Using the PCK rat model of PKD, we have identified a minimally invasive biomarker cluster with high correlative value for renal cystic index. This finding is important in that disease prognosis, patient compliance, interventional decisions and outcomes stand to be improved by regular disease monitoring. Identification of biomarkers of PKD also can better stratify transplant waitlists for kidneys or livers. Furthermore, rather than reliance upon a single biomarker, clinical outcomes may be better predicted from a cluster of disease-relevant biomarkers that correlates strongly with outcome. Clinical trials would also benefit from such biomarkers given the reluctance to invest in trials wherein clinical endpoints could be years away. Moreover, relevant patents are also discussed related to the use of renal biomarkers as diagnostics.

Keywords: Biomarker, cluster, correlation, cystic index, fibrosis, imaging, liver, polycystic kidney disease.

INTRODUCTION

Polycystic kidney disease (PKD), in its autosomal recessive (AR) or autosomal dominant (AD) form, is characterized by the formation and expansion of numerous fluid-filled cysts within the kidneys [1-4]. ARPKD, associated with *PKHD1* gene mutations, is a juvenile-type cystic disease with an incidence of 1:20,000 [1, 2]. Incidence of ADPKD, arising from mutations within either the *PKD1* or *PKD2* gene, is 1:500-1,000 [3, 4]. The majority of ADPKD cases are diagnosed between the second and fourth decade of life and progression to end-stage renal disease occurs in 50% of patients. Quite often, sequelae of both forms of PKD manifest in other organs such as the liver and pancreas. In addition to cyst formation, interstitial collagen deposition or scarring is often observed in both the kidney and the liver [1, 5]. Highly aggressive fibrocystic kidney and liver disease in ARPKD means that many children with this form of disease do not live past the age of ten years. Progressive enlargement of the kidneys via replacement of the renal parenchyma with cysts, pericystic fibrosis and decreasing renal function incriminates ADPKD as the leading genetic disposition for renal transplantation. In fact, in the absence of any effective treatments, kidney and/or liver transplantation remains the therapeutic mainstay in PKD [6, 7].

Today, a positive family history coupled with imaging remains the diagnostic mainstay for PKD [8, 9]. On the basis of safety, efficacy, compliance and reimbursement, ultrasonography is the most commonly used imaging modality to diagnose PKD. Once diagnosis is made, proper management of the patient requires monitoring of disease progression. This is especially important in anticipating patients' medical needs and in making critical and life-saving decisions such as transplant prioritization. From a classical disease pathology perspective, kidney-to-body mass ratio or renal cystic index, i.e., the total cyst space as a fraction of the renal parenchyma, are the gold standard for informing disease progression and severity [10, 11]. Accurate determination of kidney mass in a clinical setting is clearly impractical. Utilizing accurate and reliable diagnostic techniques that monitor cyst formation or growth is therefore paramount to predict the progression, the prognosis and associated complications of this disease. Although an excellent diagnostic tool, ultrasound's utility in staging the disease or evaluating disease progression is limited [12, 13], ultrasonography brings operator-bias and generates relatively poor quality images

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when compared to computed tomography (CT) or magnetic resonance imaging (MRI). Use of ultrasonography is highly questionable for detecting small but significant changes in renal volume or cysts < 1cm in diameter. Finally, the empirical formula used in ultrasound to calculate renal dimensions often results in underestimation of kidney volume [12, 13].

Finer cysts can be detected by both CT scan and MRI and are therefore also used for diagnosing and staging PKD especially when ultrasonography data are equivocal [14]. However both CT and MRI have their drawbacks in that both these procedures involve significant time, labor and cost and are impractical for serial determination of disease worsening. A major disadvantage of CT includes the risk for exposure to radiation and radiocontrast especially in children and older adults with renal insufficiency [14]. Although gadolinium-MRI has little to no renal toxicity and its sensitivity permits the detection of cysts of only 2 to 3mm in diameter [13, 15], this technology, in addition to detecting cysts associated with PKD, is likely to detect small, simple cysts unrelated to disease. Therefore, until its diagnostic value has been validated, it should not be used as the initial imaging modality for diagnosis of ADPKD. Finally, as discussed previously, both ARPKD and ADPKD can involve fibrotic scarring of the kidneys and/or liver and loss of tissue function. Currently, there is no accepted imaging modality to accurately measure fibrotic changes within the renal or hepatic parenchyma.

The PCK (PCK/CrljCrl-pkhd1pck/Crl) rat is a mammalian model of spontaneous PKD with both kidney and liver manifestations [16, 17]. Linkage and gene cloning analysis confirmed that kidney and liver disease in ARPKD patients and in PCK rats are caused by mutations to orthologous genes, *PKHD1/Pkhd1*. Although the pattern of inheritance is autosomal recessive, the PCK rat exhibits many features that resemble human ADPKD [16, 17]. Similar to human ADPKD, disease progression is more severe in males. In both the human and the PCK rat, kidneys may appear normal at birth followed by slow progression of cystic disease. The rats develop progressive cystic enlargement of the kidneys after the first week of age accompanied by inflammation and interstitial fibrosis of the kidneys and the liver.

In this study, we evaluated a panel of minimally invasive renal biomarkers and correlated the outcomes with renal cystic index in the PCK rat model of PKD. Since hepatic cysts were absent or too small to quantify accurately, hepatic biomarkers were correlated with liver-to-body mass ratio.

MATERIALS AND METHODS

Animals

All studies relating to animals were approved by our institutional animal use and care committee. Age and gender-matched Sprague-Dawley (wild-type control) and 4 week-old male PCK/CrljCrl-Pkhd1^{pck}/Crl rats were administered a standard laboratory diet and water ad libitum. A small subset of animals (PCK, n = 3; wild-type, n = 3) were sacrificed at 6.5 weeks of age to confirm disease pathology. Animals comprising a "training set" (PCK, n = 14; wild-type, n = 5) were sacrificed at ~ 13.5 weeks of age. An animal was sacrificed at 13.5 weeks which provided data for the "test data" set. Prior to sacrifice, 24hr urine was collected by housing the animals in metabolic cages. Kidney, liver and serum samples were obtained at sacrifice.

Tissue and Biomarker Analysis

Kidney, liver and body masses were measured at sacrifice. Cystic index is the percentage of the kidney occupied by cysts and was quantified in hematoxylin and eosin (H&E) stained kidney sections using digital planimetry (NIS Elements Viewer, www.nikoninstruments.com). Serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), blood urea nitrogen (BUN) and creatinine (SCr) were measured by North Shore-LIJ core lab (New Hyde Park, NY). Proteinuria was measured using a modified Bradford and Lowry Bio-Rad protein assay and expressed as mg/24 hr urine. Microalbuminuria (Abcam ELISA) was expressed as mg/24 hr urine. Levels of neutrophil gelatinase-associated lipocalin (NGAL) (BioPorto Diagnostics, www.bioporto.com), cystatin C (R&D Systems, www.rndsystems.com), interleukin-18 (IL-18) (Biomedical Assay, www.biotechist.com) and kidney injury molecule-1 (KIM-1) (BioTrend, www.biotrend.com) were determined in both serum and urine samples using an enzyme-linked immunosorbent assay (ELISA). Kidney and liver hydroxyproline, markers of tissue fibrosis, were measured from tissue homogenates and expressed as µg/kidney or µg/liver.

Data Analysis

Between group (control vs PCK) differences were analyzed by Student's T-test. A $p < 0.05$ was considered significant. To identify renal biomarkers tracking renal cystic index, a scatterplot between variables was analyzed using linear regression. Linear regression analysis ensures that the relation between biomarker and cystic index holds or is maintained across all stages of disease. A Pearson product-moment correlation coefficient $r \geq 0.7$ was used as the lower limit for biomarker inclusion. For the liver studies, a scatterplot of hepatic biomarker against liver-to-body mass was analyzed for an $r \geq 0.7$.

RESULTS

Kidney

As early as 6.5 weeks of age, kidneys from PCK rats were highly enlarged compared to age-matched Sprague-Dawley rats. Both kidney mass and kidney-to-body mass ratios were significantly exaggerated Fig. (**1**). Numerous fluid-filled cysts were evident on the surface of the kidneys from the PCK rats. The sagittal section of a wild-type and PCK kidney shown in Fig. (**2**), demonstrates the extent of disease as the renal parenchyma in the PCK rat has been replaced almost entirely by multiple small and large cysts.

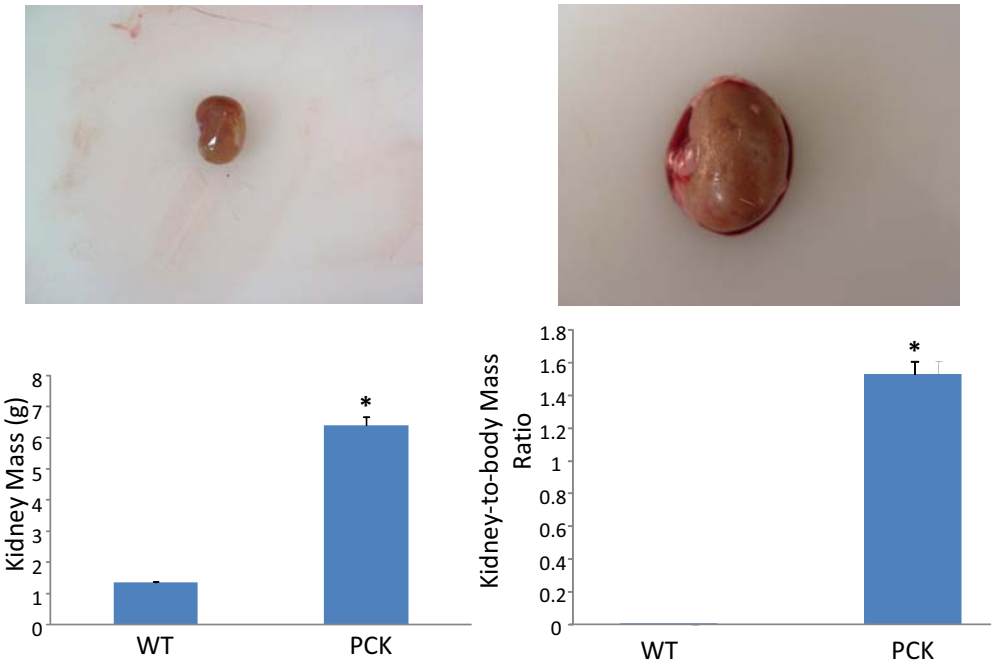

Fig. (1). Enlarged Kidneys in PCK Rats: By 6.5 weeks of age, compared to kidneys from age-matched, wild-type (WT) controls (top left), kidneys from PCK rats (top right) were enlarged with fluid-filled cysts visible on the surface. Kidney mass and kidney-to-body mass ratio were highly exaggerated compared to controls. *, $p < 0.05$ vs WT.

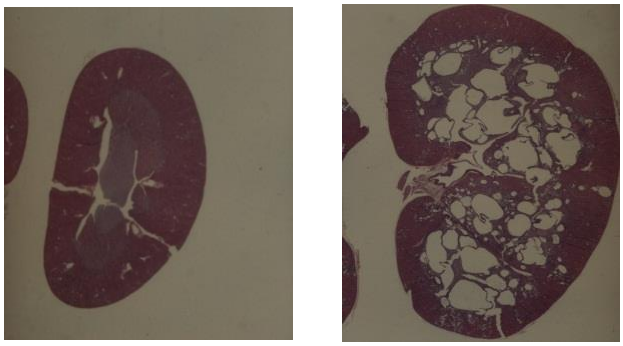

Fig. (2). Renal Cysts in PCK Rats: By 6.5 weeks of age, compared to age-matched, wild-type (WT) controls (top left), the renal parenchyma from PCK rats (top right, 20 X) was replaced by cysts.

Having confirmed disease phenotype, animals were allowed to age and were sacrificed at ~ 13.5 weeks of age. Fibrocystic kidney disease was evident in these animals given the ~30-fold increase in renal cystic index and increased renal hydroxyproline, a marker of interstitial kidney fibrosis Fig. (**3**). Consistent with the literature, PKD was associated with renal dysfunction as evidenced by increased BUN, SCr, proteinuria and albuminuria Fig. (**4**).

Clinically, PKD is frequently associated with enlarged kidneys. Using a "training set" of animals, we firstly determined whether renal cystic index correlates with kidney-to-body mass in this rat model of PKD. Renal cystic index for each animal was plotted against the corresponding kidney-to-body-mass ratio. As seen in Fig. (**5**), there is good correlation ($r = 0.76$; $p < 0.01$) between renal cystic index and kidney-to-body mass ratio. Next, we correlated each of the biomarkers listed in Table **1** with renal cystic index. While several biomarkers exhibited good correlation with cystic index, including BUN and tissue hydroxyproline (both analytes returned r values ≥ 0.7), other biomarkers did not Fig. (**6**). Table **2** ranks the correlations between the renal biomarkers evaluated andrenal cystic index.

To determine the correlative value of this cluster derived from the "training set" of animals, urine IL-18, SCr, BUN and kidney hydroxyproline were analyzed from a PCK rat that formed the "test set". Values were entered into the linear regression equations for each of the biomarkers and the calculated cystic indices averaged. Separately, cystic index was measured in H&E-stained kidney sections from this animal. As seen in Table **3**, the calculated cystic index agrees well with the measured cystic index.

Liver

As early as 6.5 weeks of age, livers from PCK rats were highly enlarged compared to age-matched Sprague-Dawley rats, and liver-to-body mass ratios were significantly exaggerated Fig. (**7**). At sacrifice at 13.5 weeks of age, although it was not possible to identify or measure hepatic cysts, given the cirrhotic appearance of the livers there was significant hepatic deposition of collagen, which was confirmed by liver hydroxyproline content as shown in Fig. (**8**). As hepatic cysts were absent at this stage or too small to quantify, scatterplots of liver-to-body mass ratio against hepatic biomarkers, liver hydroxproline, AST and ALT were made. As seen in Table **4**, liver hydroxyproline and AST correlate with hepatomegaly but ALT does not.

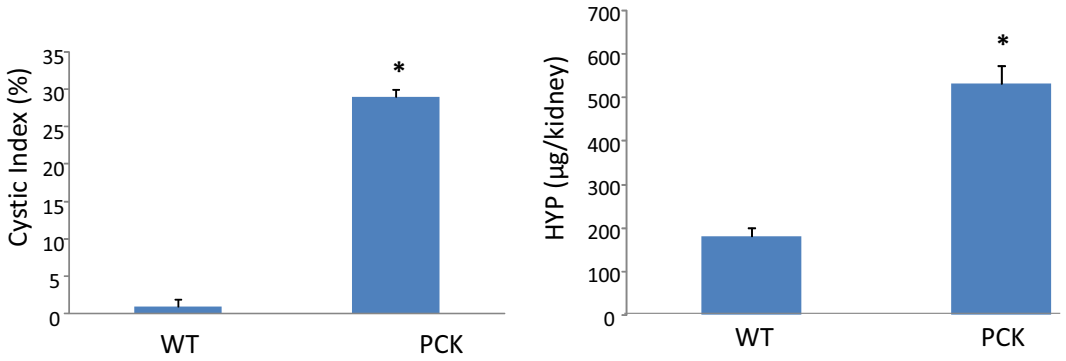

Fig. (3). Fibrocystic Kidney Disease in the PCK Rat: By 13.5 weeks of age, kidneys from PCK rats had a highly elevated cystic index. Interstitial scarring or fibrosis was evidenced by increased kidney hydroxyproline (HYP). *, $p < 0.05$ vs WT

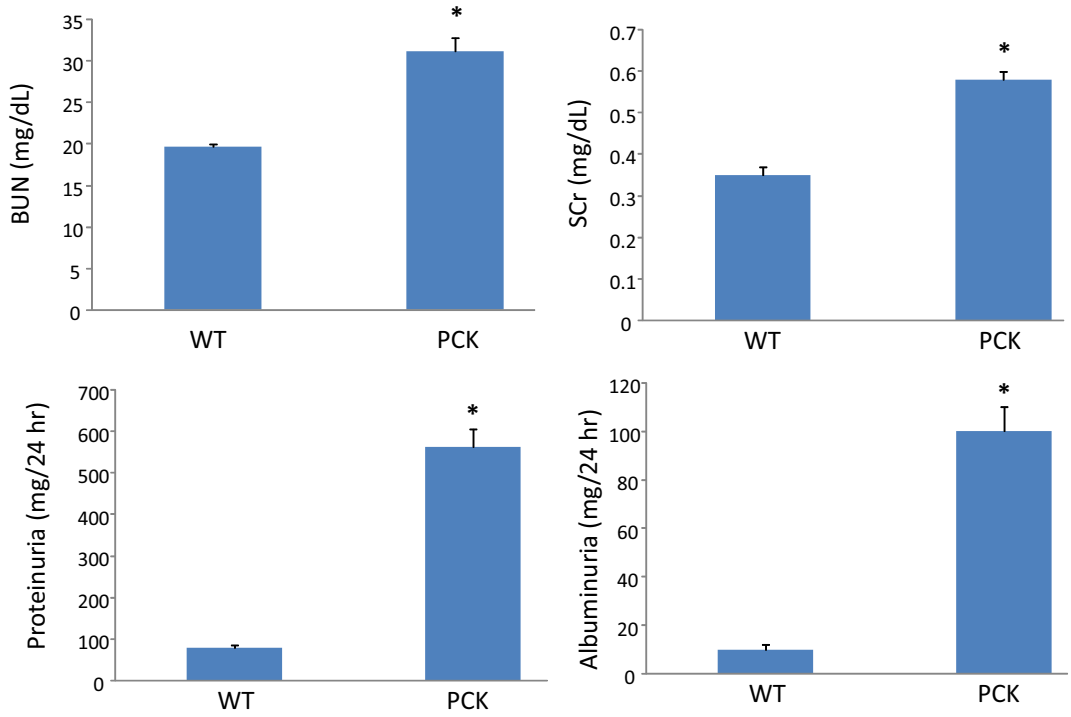

Fig. (4). Renal Dysfunction in the PCK Rat: Hallmark indices of renal dysfunction including BUN, SCr, proteinuria and albuminuria accompanied fibrocystic disease in the PCK rat *, $p < 0.05$ vs WT.

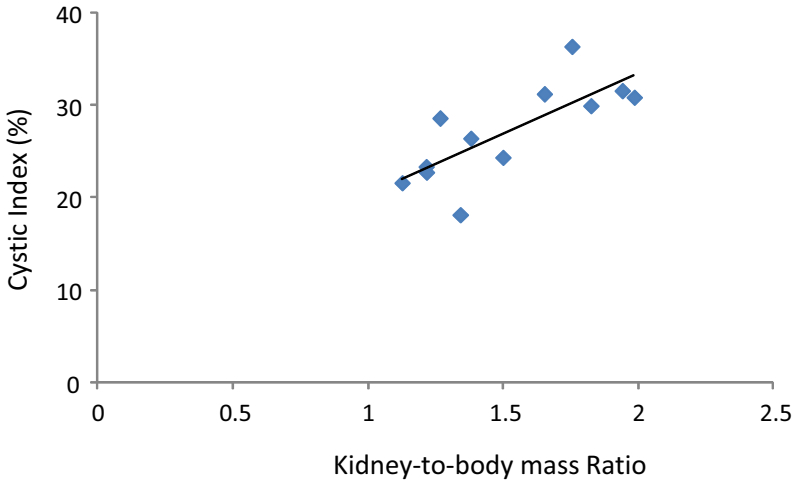

Fig. (5). Cystic Index and Kidney-to-body-mass: Consistent with the clinical picture, Increasing renal cystic index is accompanied by increasing kidney-to-body mass ratios. $r = 0.76$.

Table 1. Renal Biomarkers Evaluated : Several Minimally- or Non-Invasive but Clinically Relevant Biomarkers were Measured and Correlated with Renal Cystic Index.

Biomarker	Urine	Serum	Kidney
BUN		X	
SCr		X	
Protein	X		
Albumin	X		
NGAL	X	X	
Kim-1	X	X	
Cystatin C	X	X	
IL-18	X	X	
Collagen (HYP)			X

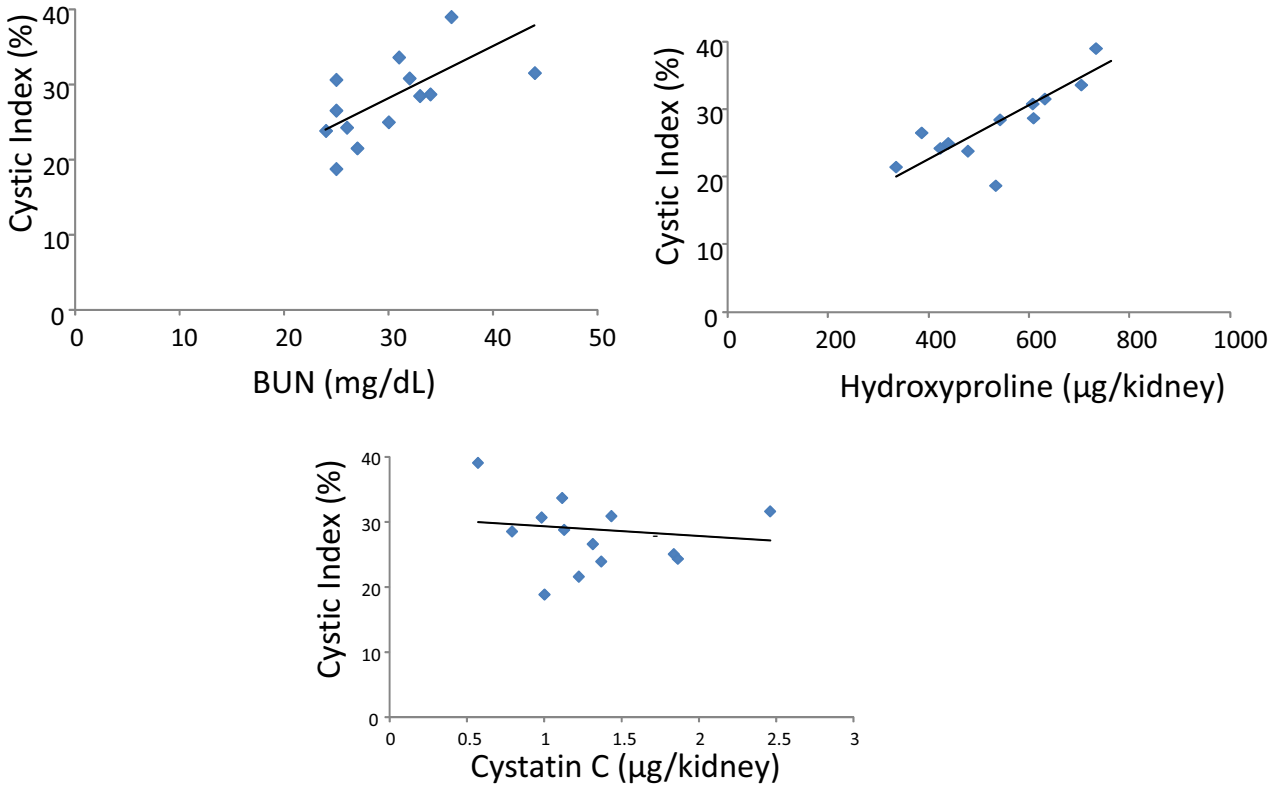

Fig. (6). Biomarkers and Renal Cystic Index Correlation: Some biomarkers returned good correlation ($r \geq 0.7$) against cystic index including BUN ($r = 0.73$) and kidney hydroxyproline ($r = -0.84$). By contrast, serum Cystatin C levels exhibited poor correlation with cystic index ($r = 0.12$).

Table 2. Renal Biomarker Cluster for PKD: BUN, SCr, Kidney Hydroxyproline and Urine IL-18 Give Good Correlation with Renal Cystic Index.

Biomarker	r	p
BUN	**0.73**	**< 0.01**
Scr	**0.7**	**< 0.05**
Kidney hrdroxyproline	**0.85**	**< 0.01**
Urine IL-18	**0.78**	**< 0.01**

Table (2) contd…

Biomarker	r	p
Serum IL-18	0.16	> 0.05
Urine NGAL	0.23	> 0.05
Serum NGAL	0.12	> 0.05
Urine KIM-1	0.48	> 0.05
Serum KIM-1	0.2	> 0.05
Urine Cystatin C	0.44	> 0.05
Serum Cystatin C	0.35	> 0.05
Proteinuria	0.6	< 0.05
Albuminuria	0.63	< 0.05

Table 3. Predictive Value of Renal Biomarker Cluster in PKD: BUN, SCr, Kidney Hydroxyproline and Urine IL-18 from the Training Set were used to Predict Cystic Index in a PCK rat. Values for Cystic Indices from the Linear Regression Equations were Averaged to Yield a Calculated Cystic Index which was then Compared with the Measured (H&E Stained Sections) Cystic Index.

Biomarker	Biomarker Level	Calculated Cystic Index	Measured Cystic Index
Urine IL-18 (µg/mL)	0.0005	37	
SCr (mg/Dl)	0.58	27	
BUN (mg/Dl)	27	25.9	
Kidney HYP (µg/Kidney)	469	25.36	
	Average	28.8	25.93

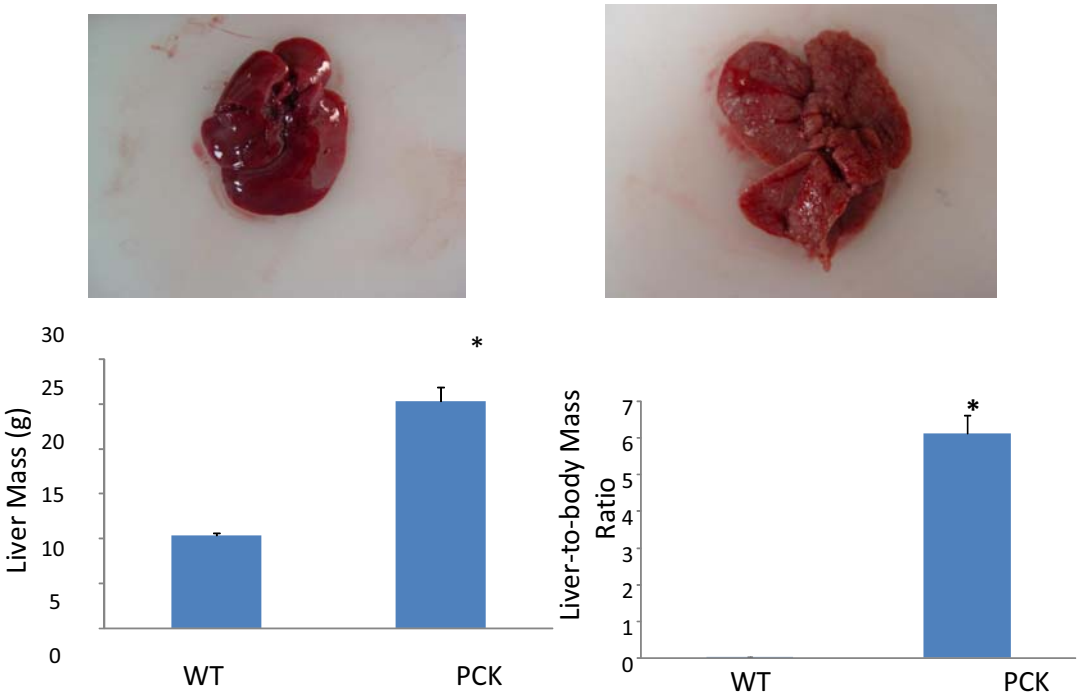

Fig. (7). Enlarged Livers in PCK Rats: By 6.5 weeks of age, compared to livers from age-matched, wild-type (WT) controls (top left), livers from PCK rats (top right) were enlarged and had a fibrotic appearance. Both the liver mass and the liver-to-body mass ratio were highly exaggerated compared to control. *, $p < 0.05$ vs WT.

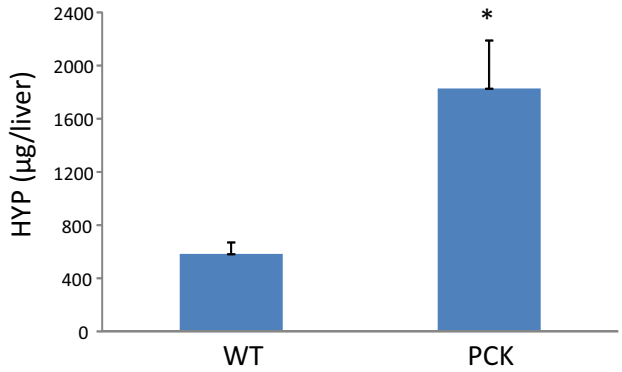

Fig. (8). Fibrotic Liver Disease in the PCK Rat: By 13.5 weeks of age, livers from PCK rats exhibited increased fibrosis evidenced by HYP accumulation. *, $p < 0.05$ vs WT.

Table 4. Hepatic Biomarker Cluster for PKD: AST and Liver Hydroxyproline give good Correlation with Liver-to-Body Mass Ratio.

Biomarker	r	p
AST	**0.86**	**< 0.01**
Liver HYP	**0.92**	**< 0.01**
ALT	0.017	> 0.05

DISCUSSION

In the PCK rat model of fibrocystic kidney and liver disease, to the best of our knowledge, for the first time we describe a biomarker cluster comprising SCr, BUN, kidney hydroxyproline and urine IL-18 levels that correlates with cystic index; AST and liver hydroxyproline form components of this cluster that correlate with hepatomegaly. In as much as renal cystic index and hepatic enlargement are measures of disease pathology in PKD, the following Hamiltonian correlates with disease severity,

$$\overline{H}_{PKD} = \left\{ \begin{matrix} BUN \\ Urine\ IL\ -18 \\ AST \end{matrix} \quad \begin{matrix} SCr \\ Kidney\ HYP \\ Liver\ HYP \end{matrix} \right\}$$

All of the renal and hepatic analytes evaluated in this study are well-characterized and are documented as biomarkers of tissue pathology and dysfunction [18]. Although not specific to any one form of kidney injury or disease, by and large, in the setting of established and recognized PKD and in the absence of any competing pathologies, this biomarker cluster tracks PKD disease severity.

Consistent with clinical reports, elevations in several serum and urine biomarkers were observed in this model of PKD [19, 20]. Also consistent with clinical findings, elevations in any given biomarker did not necessarily correlate with disease expansion. For example, in the Consortium for Radiologic Imaging for the Study of Polycystic Kidney Disease (CRISP) study [21], urine NGAL excretion rates were determined in conjunction with measures of total kidney volume and estimated glomerular filtration rate (eGFR). Although urine NGAL was mildly and stably elevated in ADPKD, it did not correlate with changes in total kidney volume or kidney function. In fact, in the present study, of the 9 renal biomarkers evaluated, only 4 correlated with cystic index. The other biomarkers, although elevated in both serum and urine, gave a poor correlation with cystic index. In the present study, it was impractical to accurately quantify hepatic cysts and hepatic cystic index. In contrast, hepatomegaly was obvious and confirmed by increased liver-to-body mass ratio. This phenomenon is frequently observed in both ARPKD and ADPKD wherein hepatic cysts form much later and after onset of hepatomegaly. In fact, both renal enlargement and hepatomegaly in the pediatric ARPKD population are primary causes of pulmonary underdevelopment and death.

Importantly and from a patient compliance perspective, the biomarkers described in this study can be obtained using minimally invasive or non-invasive procedures and in an outpatient setting. Even determination of tissue hydroxyproline can be accomplished using routine, timed biopsies. Serial measurements of these biomarkers in patients are clearly feasible and can be used to track disease progress.

This study forms the first attempt to link biomarkers to PKD disease severity, inasmuch as renal cystic index and hepatomegaly are indicative of disease severity. By no means is this cluster complete and it is certainly plausible that additional markers might find a place in this cluster. The results from this study only form a start to an unsupervised learning approach that will be required to evaluate all known renal and hepatic biomarkers and correlate it to renal cystic index and hepatomegaly. Studies in other preclinical models of PKD will need to be undertaken to confirm that this cluster is indeed applicable to clinical disease. Time-dependent measurements of this cluster in animal models will ultimately provide quantitative information correlating the magnitude of increase of each member within the cluster to the magnitude of increase in the renal cystic index. Data from serial measurements within these animal models coupled with data from human samples can be used to arrive at a formula such as the Cockroft-Gault, modified-diet-in-renal disease (MDRD) or Chronic Kidney Disease Epidemiology (CKD-EPI) equations to quantify PKD disease severity as a function of the biomarker cluster. This study sets the stage for further development of an important diagnostic tool in PKD.

RECENT PATENTS ON RENAL DISEASE BIOMARKERS

From the perspective of diagnostics providers and given the Food and Drug Administration's (FDA) increasing proclivity towards use of biomarkers as a surrogate for clinically meaningful endpoints, there is growing interest in patenting inventions that use a biomarker or combination of biomark-

ers as areadout of disease status. Several examples listed below provide insight into the growth potential of this area.

EP236437 claims a method for evaluating renal status by correlating one or more renal injury markers with threshold values to assess risk, where the marker is epidermal growth factor and optionally one or more other marker from among complement C3, interleukin-4, interleukin-1 alpha, tubulointerstitial nephritis antigen, transforming growth factor beta-1, bone morphogenetic protein 7, osteopontin, netrin-1, and growth-regulated alpha protein [22].

US8778615 claims a method for evaluating renal status by measuring the level of tissue inhibitor of metalloproteinase 2 in urine using a specific antibody, and correlating the assay result generated by the assay, in comparison to values from subjects with various levels of renal failure, to a likelihood that the subject is at risk of a future acute renal injury and directing course of treatment [23].

US20140171522 claims a method for evaluating renal status in a subject by assaying urine for one or more biomarkers among heat shock protein beta-1, WAP four-disulfide core domain protein 2, choriogonadotropin subunit beta, placenta growth factor, and mitochondrial 60 kDa heat shock protein D and comparing the results to that from predetermined populations of patients with different renal statuses [23].

EP2743702 claims a method for evaluating renal status in a subject by measuring soluble tumor necrosis factor receptor superfamily member 6 in a body fluid sample and correlating the assay results to the renal status of the subject [23].

US20140147864 claims a method for evaluating renal status in a subject at risk of a future or current acute renal injury by measuring in a urine sample one or more of proheparin-binding EGF-like growth factor, tenascin C, angiopoietin-related protein 4, fibroblast growth factor 19, fibroblast growth factor 21, heparin-binding growth factor 1, angiopoietin-related protein 6, proepiregulin, probetacellulin, amphiregulin, angiogenin, thrombospondin-2, and collagen alpha-1(XVIII) chain and comparing the result to the renal status of a predetermined subpopulation of individuals having a known predisposition of a future or current acute renal injury [24].

US20140141528 claims a method for evaluating renal status in a subject by measuring each of C-X-C motif chemokines-1, -2, and -3 and correlating the assay result with those of a predetermined subpopulation of individuals having a known predisposition of a future or current acute renal injury [25].

US20140080128 claims a method for determining whether a subject is at risk of having or developing a chronic kidney disease by measuring periostin gene mRNA and comparing it to the level from a reference level of periostin gene expression in the general population or from healthy subjects [26].

EP2661620 claims a method for evaluating renal status in a subject by measuring trefoil factor 3 in a body fluid sample, and correlating the result to risk stratification, early diagnosis, staging, prognosis, classifying and monitoring of the renal status of the subject or correlating the assay result to the renal status of the subject [24].

EP2324354 claims a method for evaluating renal status in a subject by measuring the kidney injury marker cytochrome C, and optionally further insulin-like growth factor IA; and correlating the assay result(s) to the renal status of the subject [27].

US20110207161 claim a method for evaluating renal status by assaying one or more kidney injury biomarkers among soluble CD44 antigen, Angiopoietin-1, soluble Angiopoietin-1 receptor, C-X-C chemokine motif 5, soluble Endoglin, soluble Tumor-associated calcium signal transducer 1, Erythropoietin, soluble Fractalkine, Heme oxygenase 1, soluble Interleukin-1 receptor type II, soluble Interleukin-6 receptor subunit-alpha, Lymphotactin, Lymphotoxin-alpha, Stromelysin-1, C-C motif chemokine 22, C-C motif chemokine 5, and Thrombospondin-1, and correlating the assay result(s) to the renal status of the subject [23].

EP2393937 claims a method for evaluating renal status in a subject by measuring a kidney injury marker from among Prostatic acid phosphatase, Lactotransferrin, Soluble erythropoietin receptor, Von Willebrand factor, Soluble endothelial protein C receptor, and Beta-2-glycoprotein 1 and correlating the assay result(s) to one or more of risk stratification, staging, prognosis, classifying and monitoring of the renal status of the subject [23].

US2013031670 claims a method for evaluating renal status in a subject by measuring, in a urine sample, Beta-nerve growth factor, Interleukin-17A, Follitropin subunit beta, Collagenase 3, Follistatin, Vitamin D Binding Protein, Islet amyloid polypeptide, Insulin C-peptide, Complement Factor H, Gastric inhibitory polypeptide, Glucagon-like peptide 1, Glucagon, Involucrin, Type II cytoskeletal Keratin-1/Keratin-10, Type II cytoskeletal Keratin-6A/6B/6C, Osteocalcin, Lipopolysaccharide, Pancreatic prohormone, Peptide YY, Agouti-related protein, Ciliary neurotrophic factor, Appetite-regulating hormone, Transthyretin, Insulin receptor substrate 1, and NF-kappa-B inhibitor alpha; and correlating the assay result(s) generated by the assay instrument to the renal status of the subject based on values from a predetermined subpopulation of individuals having a known predisposition of a future or current acute renal injury [28].

WO2012103450 claims a method for evaluating renal status by measuring from among Angiopoietin-related protein 3, Soluble Lymphatic vessel endothelial hyaluronic acid receptor 1, and Vascular endothelial growth factor D on a body fluid sample obtained from the subject to provide an assay result; and correlating the assay result(s) to the renal status of the subject [24].

WO2014028338 claims a method for evaluating renal status in a sepsis patient by measuring hyaluronic acid in a body fluid sample; and correlating the assay result(s) to the renal status of the sepsis patient [29].

CONCLUSION

We present for the first time a unique cluster of biomarkers that correlates with renal cystic index and hepatomegaly in a rodent model of PKD. Further development and clinical validation of this biomarker cluster can serve as an important tool to track disease progression in PKD.

CURRENT & FUTURE DEVELOPMENTS

Studies in other preclinical models of PKD, including murine models, will need to be undertaken to verify that this cluster, or a more refined cluster, is indeed applicable to clinical disease. The fully developed cluster will need to be tested in a prospective clinical trial and in existing clinical PKD databases comprising serum, urine and biopsy samples, as a first step toward routine clinical use in patients presenting with PKD.

CONFLICT OF INTEREST

Ping Zhou, Latha Paka, Itzhak D. Goldberg and Prakash Narayan, are stock or stock option holders in Angion Biomedica Corp.

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SUPPLEMENTARY MATERIAL

Supplementary material is available on the publisher's website along with the published article.

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