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CLINICAL RESEARCH

Urinary Biomarkers Identify Autosomal Dominant Polycystic Kidney Disease Patients With a High Likelihood of Disease Progression

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Introduction: The variable disease course of autosomal dominant polycystic kidney disease (ADPKD) makes it important to develop biomarkers that can predict disease progression, from a patient perspective and to select patients for renoprotective treatment. We therefore investigated whether easy-to-measure urinary biomarkers are associated with disease progression and have additional value over that of conventional risk markers.

Methods: At baseline, inflammatory, glomerular, and tubular damage markers were measured in 24-hour urine collections (albumin, IgG, kidney injury molecule−1 (KIM-1), *N*-acetyl-β-D-glucosaminidase (NAG), β2 microglobulin (β2MG), heart-type fatty acid binding protein (HFABP), macrophage migration inhibitory factor (MIF), neutrophil gelatinase-associated lipocalin (NGAL), and monocyte chemotactic protein−1 (MCP-1). Disease progression was expressed as annual change in estimated glomerular filtration rate eGFR (Chronic Kidney Disease EPIdemiology equation), measured glomerular filtation rate (mGFR) (using ^{125}I-iothalamate), or height-adjusted total kidney volume (htTKV). Multivariable linear regression was used to assess associations of these markers independent of conventional risk markers.

Results: A total of 104 ADPKD patients were included (40 ± 11 years, 39% female, eGFR 77 ± 30, mGFR 79 ± 30 ml/min per 1.73 m^2 and htTKV 852 [510−1244] ml/m). In particular, β2MG and MCP-1 were associated with annual change in eGFR, and remained associated after adjustment for conventional risk markers (standardized β = −0.35, $P = 0.001$, and standardized β = −0.29, $P = 0.009$, respectively). Adding β2MG and MCP-1 to a model containing conventional risk markers that explained annual change in eGFR significantly increased the performance of the model (final $R^2 = 0.152$ vs. 0.292, $P = 0.001$). Essentially similar results were obtained when only patients with an eGFR ≥ 60 ml/min per 1.73 m^2 were selected, or when change in mGFR was studied. Associations with change in htTKV were less strong.

Discussion: Urinary β2MG and MCP-1 excretion were both associated with GFR decline in ADPKD, and had added value beyond that of conventional risk markers. These markers therefore have the potential to serve as predictive tools for clinical practice.

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The age at which patients with autosomal dominant polycystic kidney disease (ADPKD) will reach end-stage kidney disease (ESKD) shows large interindividual variability,[1] even between family members that share the same mutation.[2] Predicting the rate of disease progression has become important, now that the first therapeutic options for ADPKD have emerged.[3,4] Especially patients with a high likelihood of rapid disease progression should be selected for treatment, because in such patients the benefit-to-risk ratio of treatment is expected to be optimal.[5,6]

Currently, several variables are available to predict disease progression in ADPKD. Glomerular filtration

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rate (GFR) indexed for age is a strong predictor but is less sensitive in early stages of this disease, when GFR can remain in the normal range due to compensatory hyperfiltration, while cysts are progressively formed.[1] Therefore, much attention has been focused on total kidney volume (TKV) as a predictor.[1,7] Furthermore disease progression is influenced by the ADPKD genotype, with patients with a *PKD1* mutation, especially truncating mutations, progressing faster toward ESKD compared to patients with a *PKD2* mutation.[2] However, assessment of TKV and genotype is laborious and expensive, and their associations with the rate of disease progression are limited at an individual patient level. Therefore, new risk markers need to be developed that, either alone or in combination with conventional risk markers, can predict the rate of disease progression in ADPKD.

Because ADPKD is a tubular disease with an inflammatory component, measurement of urinary tubular damage and inflammation markers is of interest, especially because these markers are relatively inexpensive and easy to measure. Several cross-sectional studies have shown that these markers are associated with ADPKD severity, assessed as GFR and TKV.[8–11] In this study, we aimed to determine, in a longitudinal setting, whether urinary tubular damage and inflammation markers are associated with rate of ADPKD progression assessed as annual change in GFR and TKV, and whether these markers have added value beyond that of currently used risk markers.

METHODS

Setting and Subjects

From January 2007 until September 2012, a total of 133 ADPKD patients from the University Medical Center Groningen were included in an observational study. The diagnosis of APDKD was made based upon the revised Ravine criteria.[12] Patients were considered ineligible if they received kidney replacement therapy, had undergone kidney surgery, were unable to undergo magnetic resonance imaging, or had other systemic diseases or used treatments or medications potentially affecting kidney function, such as calcineurin inhibitors or nonsteroidal anti-inflammatory drugs (NSAIDs).[9,10] For the present study, 29 patients were excluded because they had a follow up time $<$ 1 year, leaving 104 patients for analysis. The study was performed in adherence to the Declaration of Helsinki, and all participants gave written informed consent. The institutional review board deemed this study exempt from assessment because of its post hoc exploratory nature.

Measurements

At the baseline visit, a physical examination was performed, including blood pressure measurements. Fasting blood samples were drawn for the measurement of creatinine and *PKD* mutation analyses. The estimated GFR (eGFR) was calculated using the 2009 Chronic Kidney Disease EPIdemiology (CKD-EPI) equation.[13] The *PKD* mutation analysis was performed with DNA isolation using PUREGENE nucleic acid purification chemistry on the AUTOPURE LS 98 platform (Qiagen), followed by sequencing of amplified coding exons directly (exons 34−46), or on long-range polymerase chain reaction products (exons 1−33).[14] In addition, measured GFR (mGFR) was determined by a constant infusion method with ^{125}I-iothalamate, and magnetic resonance imaging was performed to assess TKV, using a standardized abdominal magnetic resonance imaging protocol without the use of intravenous contrast. TKV was measured on T2-weighted coronal images using Analyze direct 9.0 (AnalyzeDirect, Inc., Overland Park, KS) by classical volumetry (i.e., manual tracing) and adjusted for height (htTKV).

The day before the baseline visit, patients collected a 24-hour urine, of which samples were stored frozen at −80°C that were used to measure albumin as a general kidney damage marker; immunoglobulin G (IgG) as a glomerular damage marker; and β2 microglobulin (β2MG), kidney injury molecule−1 (KIM-1), and *N*-acetyl-β-D-glucosaminidase (NAG) as proximal tubular damage markers; heart-type fatty acid binding protein (HFABP) as a distal tubular damage marker; and macrophage migration inhibitory factor (MIF), neutrophil gelatinase-associated lipocalin (NGAL), and monocyte chemotactic protein−1 (MCP-1) as inflammation markers.[15–23]

Urinary albumin was determined by immunonephelometry (BNII; Dade Behring Diagnostics, www.dadebehring.com). Urinary IgG, HFABP (Hytest, www.hytest.fi), β2MG (Anogen, www.yesbiotech.com), KIM-1, MIF, NGAL, and MCP-1 (R&D Systems, www.rndsystems.com) were measured by enzyme-linked immunosorbent assay. NAG was measured with a modified enzyme assay according to Lockwood and corrected for nonspecific conversion (HaemoScan, www.haemoscan.com). Urine samples were diluted twice for KIM-1, β2MG, MCP-1, and MIF, 5 times for HFABP, and 100 times for NGAL and IgG. Detection limit for albumin was 0.003 mg/ml, for IgG 220 ng/ml, for β2MG 18 ng/ml, for KIM-1 0.087 ng/ml, for HFABP 0.38 ng/ml, for MIF 0.06 ng/ml, for NGAL 22 ng/ml, and for MCP-1 0.04 ng/ml. The intra- and interassay coefficients of variation were 2.2% and 2.6% for albumin, 6.3% and 8.5% for β2MG, 7.4% and 14.5% for KIM-1, 3.1% and 13.7% for NAG, 9.3% and 17.6%

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