A prospective study of multiple protein biomarkers to predict progression in diabetic chronic kidney disease

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ABSTRACT

Background. Diabetic nephropathy imposes a substantial cardiovascular and renal burden contributing to both morbidity and excess mortality. Progression of chronic kidney disease (CKD) in diabetes mellitus is variable, and few biomarkers are available to predict progression accurately. Identification of novel predictive biomarkers may inform clinical care and assist in the design of clinical trials. We hypothesized that urinary and plasma protein biomarkers predict CKD progression independently of the known clinical markers such as albuminuria and estimated glomerular filtration rate (eGFR) in diabetic nephropathy.

Methods. We studied 67 US veterans with CKD due to type 2 diabetes mellitus and 20 age-matched controls (no CKD, hypertension or cardiovascular disease). After clinical evaluation and the collection of blood and urine specimens for 24 biomarkers, we followed subjects prospectively for the next 2–6 years. CKD progression was defined in three ways: (i) clinically by examining eGFR versus time plots for each individual (slope progression), (ii) progression to end-stage renal disease (ESRD) and (iii) a composite outcome of ESRD or death.

Results. Among 17 urinary and 7 plasma biomarkers evaluated, the relationship of the biomarkers with outcome was as follows: (i) for progression identified by eGFR plots, urinary C-terminal fibroblast growth factor (FGF)-23 emerged to have the strongest primary association (adjusted odds ratio [aOR] 2.08, P = 0.008); (ii) for ESRD, plasma vascular endothelial growth factor (VEGF) had an association (aOR: 1.44, P = 0.027) and (iii) for the composite outcome of death and ESRD, plasma C-terminal FGF-23 also had a robust direct association (aOR: 3.07, P = 0.008).

Conclusion. The relationship of biomarkers with future progression of CKD is complex and depends in part on how CKD progression is defined. Biomarkers in the FGF-23 and VEGF-A pathways predicted patient progression independently of albuminuria levels in this patient cohort. Additional studies in other cohorts will help further validate this pilot study.

Keywords: albuminuria, biomarkers, chronic kidney disease

INTRODUCTION

Diabetic kidney disease in the USA has increased from an estimated 3.9 million adults during 1988–94 to 6.9 million during 2005–08 [1]. Chronic kidney disease (CKD) accounts for much of the increased mortality [2] and cardiovascular morbidity [3] associated with type 2 diabetes. Compared with CKD without diabetes, the care of CKD patients with diabetes mellitus is more costly [4]; end-stage renal disease (ESRD) care among these patients accounts for a major medical and financial burden to society [5]. No new proven therapy for established diabetic kidney disease has been developed in more than a decade, and efforts to reduce progression of ESRD have been hampered by a lack of biomarkers to reliably predict hard outcomes. Currently, the best biomarker to predict progression of diabetic CKD to ESRD remains the presence and the severity of albuminuria [6]. However, based on NHANES data estimating disease prevalence in the USA, no albuminuria was noted in an estimated 2 million of the 6.9 million prevalent patients [1]. Nonetheless, many such individuals progress to ESRD [7]. Thus, development of biomarkers other than albuminuria is needed to predict CKD progression [8, 9].

Twenty-four biomarkers that reflect the pathophysiology of CKD, through inflammation, fibrosis, angiogenesis, tubular damage and podocyte injury, were selected to establish their ability to predict patient outcomes independent of albuminuria. Many of these biomarkers were previously reported to predict CKD progression, but there are few reports that compare this large number of biomarkers in a single patient cohort. Furthermore, progression of CKD has been defined in
multiple ways. In clinical trials, a composite of ESRD and death (or cardiovascular death) is the end point that is commonly accepted as measure of a ‘hard’ outcome by regulatory bodies [10–12]. In this pilot study, we first examined the levels of biomarkers in controls and cases. Next, we evaluated the inter-relationships among the biomarkers. Finally, we hypothesized that (i) specific urinary and plasma protein biomarkers predict progression of CKD and (ii) these biomarkers would provide added predictive value to known clinical markers such as albuminuria and estimated glomerular filtration rate (eGFR).

MATERIALS AND METHODS

This study was approved by the institutional review board, and all subjects signed written informed consent. Conceptually, the study has three parts. Part 1 of the study compares each of the biomarkers among patients with CKD and diabetes with a control group without CKD and diabetes. Part 2 explores the relationship among the biomarkers. Part 3 examines the association of each of the 24 biomarkers with CKD progression.

Subject characteristics and follow-up

Subjects in this study were recruited between June 2007 and September 2011 from the renal clinic at the VA Medical Center, Indianapolis, IN, USA. Cases were patients diagnosed with diabetic nephropathy based on clinical criteria, i.e. long-standing type 2 diabetes mellitus, nephromegaly, retinopathy and sometimes kidney biopsy. To qualify for inclusion, all cases had to have a seated clinic blood pressure (BP) of <140/90 mmHg. Control subjects were recruited from the general medicine clinic at the same center. These subjects did not have hypertension, diabetes mellitus or cardiovascular disease. During a research visit, medical history was obtained and physical examination was performed. Subjects were seen every 2 years for up to 6 years. Urinary biomarkers (n = 17) and plasma biomarkers (n = 7) were selected based on review of the literature indicating a possible association with progression of CKD (Table 1). Technical details of biomarker assay analysis by enzyme-linked immunosorbent assay are provided in the Supplementary Data, Appendix. To our knowledge, these markers are not available as a protein microarray.

Outcome definitions

Slope progression. To establish a discrete change in eGFR such as by doubling of baseline serum creatinine requires that the subject is reassessed over a short period of time, typically in 4–8 weeks, to establish that the doubling of serum creatinine is persistent and not due to reversible causes such as volume depletion, nephrotoxicity, obstruction, etc. [11, 12]. Because this was an observational study with infrequent visits and subjects were only required to be seen biannually, we did not use time to doubling of serum creatinine as an outcome marker.

CKD progression by eGFR slopes was defined by plotting and examination of the slopes after collection of the biomarker. Although serum creatinine measurements were required biannually, many more serum creatinine concentration results from the hospital records were available during the course of the follow-up. These data were plotted and subjects identified to progress or not based on inspection of these plots (individual examples are shown in the Supplementary Data, Appendix). Because patients may have non-linear trajectories of eGFR change, we did not use linear regression to estimate slopes for an individual patient [13].

ESRD and death. ESRD was defined as receipt of sustained dialysis. A temporary dialysis procedure was not counted as ESRD. The date of first chronic dialysis was the date of ESRD. Death was established by querying the hospital records or the social security death index if the subject had moved out of the area. There were no cases that were lost to follow-up for these ‘hard’ outcomes.

Table 1. Individual biomarkers measured in plasma or urine

<table>
<thead>
<tr>
<th>Biomarker Urine Plasma Category</th>
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<tbody>
<tr>
<td>Vascular endothelial growth factor A (VEGF-A)</td>
</tr>
<tr>
<td>Fibronectin</td>
</tr>
<tr>
<td>Matrix metalloproteinase-7 (MMP-7)</td>
</tr>
<tr>
<td>Collagen IV</td>
</tr>
<tr>
<td>High molecular weight (HMW) Collagen IV</td>
</tr>
<tr>
<td>Connective tissue growth factor (CTGF)</td>
</tr>
<tr>
<td>Cystatin C</td>
</tr>
<tr>
<td>Nephrin</td>
</tr>
<tr>
<td>Podocalyxin</td>
</tr>
<tr>
<td>Soluble tumor necrosis factor receptor 1 (sTNF R1)</td>
</tr>
<tr>
<td>Soluble tumor necrosis factor receptor 2 (sTNF R2)</td>
</tr>
<tr>
<td>Monocyte chemotactic protein 1 (MCP-1)</td>
</tr>
<tr>
<td>Tenascin C</td>
</tr>
<tr>
<td>Fibroblast growth factor-23 C-terminus (FGF 23)</td>
</tr>
<tr>
<td>Beta-2 microglobulin (B2M)</td>
</tr>
<tr>
<td>Neutrophil gelatinase-associated lipocalcin (NGAL)</td>
</tr>
<tr>
<td>Liver-type fatty acid-binding protein (L-FABP)</td>
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</tbody>
</table>

Statistical analysis

Urinary biomarkers were normalized to milligrams of urinary creatinine. To approximate normal distribution, all biomarkers were log 2 transformed. Baseline biomarker concentrations between cases and controls were compared using an unpaired t-test. To display concentrations of these biomarkers between groups, we show medians, 25 percentile and 75 percentiles.

The relationship between various biomarkers was evaluated using hierarchical agglomerative cluster analysis. Dissimilarity between biomarkers was measured by Euclidean distance and

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average linkage to evaluate the grouping of biomarkers. A dendrogram was created to demonstrate the hierarchical relationship between biomarkers.

Longitudinal renal outcomes measured over a 2- to 6-year follow-up were progression assessed by slope, ESRD or a composite of ESRD and death. For each of these dichotomous outcomes, we performed a logistic regression analysis with the log-2-transformed biomarker as the predictor. These unadjusted analyses were next adjusted for log-2 urinary albumin/creatinine ratio. They were further adjusted for baseline eGFR when death and/or ESRD were the outcomes. Albuminuria and eGFR are the most important predictive variables for CKD progression, and they were chosen a priori. We did not further adjust for other confounders given the limited number of events in our sample. The P-values generated from these analyses were adjusted using the Holm-Sidak test for multiple comparisons. All analyses were performed using Stata 11.2 (StataCorp LP, College Station, TX).

RESULTS

The demographic and clinical characteristics of the 67 patients with diabetes mellitus and CKD, and 20 normal controls, are shown in Table 2. The study population was mostly men and about a seventh were black. Control subjects almost exclusively had an eGFR above 60 mL/min/1.73 m² and displayed no albuminuria. In contrast, all but five CKD patients had reduced eGFR and 69% had micro- or overt albuminuria. Patients on average were also significantly older, with larger body size and had a higher BP, higher HgbA1c and lower hemoglobin. Although no control subject had antihypertensive drug use (two used α-blockers for urinary outlet symptoms), the average number of antihypertensive drugs used among subjects with CKD was 3.3 ± 1.6. Of the antihypertensive drugs, β-blockers were used in 47 (70.1%), angiotensin converting enzyme (ACE) inhibitors in 38 (56.7%) and angiotensin receptor blockers in 18 (26.9%). The eGFR in cases was 43 mL/min/1.73 m², and albuminuria averaged 405 mg/g creatinine. Of the case subjects who had Stage 2 CKD, overt albuminuria was present in all. At baseline, high cardiovascular comorbidity was seen: angina (n = 25, 37%), congestive heart failure (n = 16, 23.9%), coronary revascularization (n = 27, 40.3%), myocardial infarction (n = 26, 38.8%), peripheral vascular disease (n = 19, 28.4%) and stroke (n = 14, 20.9%). Controls did not have any vascular disease, by study design. Over the 2- to 6-year follow-up (median 1.83 years), cardiovascular and renal events were seen in several participants as follows: stroke (n = 2, 3%), myocardial infarction (n = 5, 7.5%), congestive heart failure (n = 4, 6%), ESRD (n = 9, 13.4%) and death (n = 16, 23.9%). Progression of CKD as defined by eGFR slopes was seen in 37 of 67 (55%) patients. The individual trajectories of 30 non-progressors and 37 progressors are shown in the Supplementary data, Appendix.

Figure 1 shows the median (circle) and interquartile range (whiskers) of urinary biomarkers for cases and controls. Nine urinary biomarkers emerged that were significantly different between cases and controls (unadjusted P < 0.05) (Figure 1) and the remaining eight were not (Figure 2). All seven plasma biomarkers were significantly different between cases and controls (Figure 3).

The relationships among the complete set of the various urinary and plasma biomarkers are shown in Figure 4. The dendrogram demonstrates that the urinary albumin/creatinine ratio and plasma cystatin C (a marker of GFR) rest on the most extreme ends of the spectrum of relatedness. Some inflammation and fibrosis biomarkers were closely related, but others were distant. Figure 5 shows the relationships among urinary biomarkers. The urinary albumin/creatinine ratio was most distantly related to the urinary β2-microglobulin (B2M)/creatinine ratio. Surprisingly, urinary podocalyxin and nephrin, markers of podocyte injury, were quite distant from the urinary albumin/creatinine ratio. Putative inflammation markers such as urinary soluble tumor necrosis factor receptor I and urinary monocyte chemotactic protein-1 were on the opposite sides of the dendrogram. Figure 6 shows the inter-relationships among the plasma biomarkers. There appeared to be three distinct clusters: filtration marker (cystatin C), tubular markers (neutrophil gelatinase-associated lipocalcin [NGAL], fibroblast growth factor 23 [FGF23] C-terminus) and inflammation/angiogenesis markers (sTNFR1, sTNFR2, vascular endothelial growth factor-A [VEGF-A] and B2M).
The unadjusted relationship of blood and urine biomarkers with the individual outcomes, CKD progression (assessed by slope of eGFR loss), ESRD or the composite of ESRD and death, was determined (Figure 7). The largest number of significantly positive biomarkers was found for ESRD, followed by CKD progression, and then a composite of ESRD and death.

**FIGURE 1:** Urinary concentration of biomarkers between cases and controls plotted on a log scale. Circles and triangles represent the median and the error bars of the bottom and top quartiles, respectively. The P-values at the bottom of the graph represent the significance level of between-group differences. sTNF, soluble tumor necrosis factor; R1, receptor 1; R2, receptor 2; HMW, high molecular weight; Col, collagen; CTGF, connective tissue growth factor.

**FIGURE 2:** Urinary concentration of biomarkers between cases and controls plotted on a log scale. Circles and triangles represent the median and the error bars of the bottom and top quartiles, respectively. The P-values at the bottom of the graph represent the significance level of between-group differences. MMP, matrix metalloproteinase; VEGF, vascular endothelial growth factor; NGAL, neutrophil gelatinase-associated lipocalcin; FGF-23 C-ter, fibroblast growth factor 23 C-terminal; L-FABP, liver-type fatty acid-binding protein; MCP-1, monocyte chemotactic protein-1 or chemokine (C-C motif) ligand 2 (CCL2).
**FIGURE 3:** Plasma concentration of biomarkers between cases and controls plotted on a log scale. Circles and triangles represent the median and the error bars of the bottom and top quartiles. The P-values at the bottom of the graph represent the significance level of between-group differences and are all significant. sTNF, soluble tumor necrosis factor; R1, receptor 1; R2, receptor 2; NGAL, neutrophil gelatinase-associated lipocalcin; FGF-23 C-ter, fibroblast growth factor 23 C-terminal; VEGF, vascular endothelial growth factor.

**FIGURE 4:** Dendrogram for urinary and plasma biomarker derived from cluster analysis in subjects with CKD. Including subjects without CKD in the cluster analysis did not alter the matrix dissimilarity.
FIGURE 5: Dendrogram for urinary biomarker derived from cluster analysis in subjects with CKD.

FIGURE 6: Dendrogram for plasma biomarker derived from cluster analysis in subjects with CKD.
death. Although the log-2 urine albumin/creatinine ratio was a strong predictor of CKD progression as defined by the slope (OR: 1.65, 95% CI: 1.29–2.04, P < 0.001) and ESRD (OR: 1.58, 95% CI: 1.12–2.21, P < 0.01), it only marginally predicted the composite end point of death or ESRD (OR: 1.18, 95% CI: 0.97–1.44, P = 0.099). In addition, for ESRD, the baseline eGFR was an independent predictor of ESRD per milli-liter drop in eGFR 1.11 (95% CI: 1.02–1.21, P = 0.018) as was the albumin/creatinine ratio (OR for log-2 urine ACR: 1.52, 95% CI: 1.04–2.24, P = 0.032).

After adjustment for log urine albumin/creatinine for all end points and also baseline eGFR in the case of the outcomes of death and/or ESRD, only one biomarker remained significant for each of the three outcomes (Figure 8). For the composite end point of death and ESRD, plasma C-terminal FGF-23 had an association (aOR: 3.07, P = 0.008 adjustments: eGFR, log urine albumin/creatinine). For ESRD alone, plasma VEGF-A had a direct association (OR: 1.44, P = 0.027; adjustment: log urine albumin/creatinine, eGFR). For progression assessed by the slope of eGFR loss over time, urinary C-terminal FGF-23 had a direct association (aOR: 2.08, P = 0.008; adjustment: log urine albumin/creatinine). The level of biomarker concentration in diabetic CKD may be higher than normal controls (plasma FGF-23), lower than normal (plasma VEGFA) or no different from normal (urinary FGF-23). Despite baseline urinary C-terminal FGF-23 being not different between controls and CKD cases, it was strongly and independently associated with progression. Thus, cross-sectional studies comparing controls and cases are insufficient for predicting renal outcomes.

In a review associating biomarkers with progression of CKD, Fassett et al. [9] tabulated 48 studies that measured biomarkers and associated them with kidney disease progression. Only one of these studies measured multiple markers (inflammation and coagulation cascade) and associated them with progression [14]. There are several ongoing multi-marker strategies that are investigating predictive biomarkers with cardiovascular morbidity and mortality in CKD; Fassett et al. [9] tabulated 12 such studies. Our study is among the few that measure multiple biomarkers and associate them with outcomes that are relevant for clinical trials.

When evaluating the relationship of biomarkers with outcome without adjusting for other factors, many emerged as predictors of outcome (unadjusted analysis, Figure 7). However, this relationship may simply be due to intrinsic

**DISCUSSION**

Compared with controls, we determined that several biomarkers in urine and plasma were associated with diabetic kidney disease. To explore the association of kidney disease progression and biomarkers further, we evaluated the relationship between these biomarkers and long-term outcomes. This relationship between individual biomarkers and long-term outcome was confounded by how the outcome was precisely defined. Although several biomarkers were predictive of progression, only one biomarker was found that was independent of previously established clinical markers such as albuminuria and baseline eGFR. Furthermore, surprisingly, the predictive biomarkers identified were dependent on how progression of CKD was defined. For the composite end point of death or ESRD, plasma C-terminal FGF-23 had an association (aOR: 3.07, P = 0.008 adjustments: eGFR, log urine albumin/creatinine). For ESRD alone, plasma VEGF-A had a direct association (OR: 1.44, P = 0.027; adjustment: log urine albumin/creatinine, eGFR). For progression assessed by the slope of eGFR loss over time, urinary C-terminal FGF-23 had a direct association (aOR: 2.08, P = 0.008; adjustment: log urine albumin/creatinine). The level of biomarker concentration in diabetic CKD may be higher than normal controls (plasma FGF-23), lower than normal (plasma VEGFA) or no different from normal (urinary FGF-23). Despite baseline urinary C-terminal FGF-23 being not different between controls and CKD cases, it was strongly and independently associated with progression. Thus, cross-sectional studies comparing controls and cases are insufficient for predicting renal outcomes.

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When evaluating the relationship of biomarkers with outcome without adjusting for other factors, many emerged as predictors of outcome (unadjusted analysis, Figure 7). However, this relationship may simply be due to intrinsic
kidney damage represented by reduced eGFR or albuminuria. Both of these established markers are in wide clinical use and must be adjusted for when evaluating new predictive biomarkers. After adjusting for these variables, only a few biomarkers emerged. Even then, there is risk of false discovery due to multiple comparisons of biomarkers. After adjustment for multiple comparisons, the mineral metabolism pathway of FGF-23 remained significant.

We identified two markers, plasma and urinary FGF-23, being predictive of CKD progression. In our laboratory, despite 24.3% variability in measurement of replicate samples in urinary FGF-23, which should bias the results to the null hypothesis, we found an independent effect of urinary FGF-23 with progression defined by slopes. FGF-23 produced by osteocytes and osteoblasts, functions to inhibit the synthesis of 1,25-dihydroxyvitamin D3 and induce phosphaturia [15]. Parathyroid hormone acts directly on osteocytes to increase FGF-23 expression [15]. Prolonged oral phosphorus load (though a change in the ratio of inorganic phosphate to pyrophosphate in the bone), dietary vitamin D, calcium intake, metabolic acidosis and iron depletion also increase FGF-23 expression [15]. Several of these factors may accelerate the demise of kidney function, thus making the link between elevated FGF-23 and outcomes plausible.

In support of the above findings, Fliser et al. [16] have demonstrated that an elevated plasma concentration of intact or C-terminal FGF-23 was associated with increased risk of death or ESRD evaluated as a composite end point in Veterans, although this marker was not independently associated with ESRD as a sole end point. When evaluating progression by eGFR slope alone, an independent and expected direct relationship with urinary C-terminal FGF-23 emerged. Progression as defined by the eGFR slope is more analogous to doubling of serum creatinine and is supportive of data of Fliser et al. [16]. Among veterans with a similar extent of CKD as investigated here, we have previously reported that certain biomarkers may have opposite effects on death and ESRD [18]. For example, increased systolic BP is associated with increased hazards of ESRD but reduced hazard of death [18]. Similar effects may be operative in the case of FGF-23 and will require validation in future trials.

We also found that increasing plasma VEGF-A concentration was independently associated with increased risk of ESRD. VEGF is induced by hypoxia and acts on the tyrosine kinases Flt-1 (VEGFR-1) and Flk-1/KDR (VEGFR-2), which are high-affinity VEGF receptors [19]. VEGF is expressed in the retina and glomeruli and has been implicated in the pathogenesis of diabetic retinopathy and nephropathy. The VEGF system represents a complex biology. Circulating VEGF-A concentration and even local VEGF-A concentrations may not fully represent intrinsic activity in the kidney. For example, studies of kidney biopsy among patients with diabetic nephropathy demonstrated that although VEGF expression is increased in all diabetic glomeruli, the expression of VEGF receptor is increased in the endothelium of mildly injured glomerular capillaries [20]. Excessive VEGF activity increases blood flow to and the permeability of the glomerulus, amplifies the inflammatory cascade and causes destruction of the epithelial cells, podocytes and mesangial cells [21]. These

FIGURE 8: Adjusted relationship of biomarkers with outcomes: CKD progression by slope (green symbols), ESRD (red symbols) and the composite of ESRD and death (black symbols). Adjustments were made for log urinary albumin to creatinine ratio for all outcomes and baseline eGFR for ESRD and ESRD and death outcomes.
effects could culminate in glomerulosclerosis and provide a biologically plausible link between increased VEGF-A concentration and ESRD. However, other scenarios are possible. Recently, Warren et al. [22] reported that endothelial cells from a mouse model of diabetes mellitus demonstrated reduced cell surface abundance of VEGFR2 and responsiveness to VEGF. Activation and subsequent degradation of VEGFR2 were due to reactive oxygen species that can be generated in response to hyperglycemia especially among patients with CKD. The increased VEGF noted in our study may therefore represent a homeostatic response to the depletion of VEGFR2. Finally, VEGF measured in the plasma may be bound to sFlt-1, making its bioavailability poor at the receptor; in fact there was no difference in the urinary excretion of VEGFA making this scenario plausible. Thus, whether VEGF should be supplemented or inhibited cannot be answered by our study.

There are several limitations of our study. Our sample size was small and numerous biomarkers were tested; however, to minimize the risk of false discovery, results were adjusted statistically with the Holms-Sidak test. Because we did not measure biomarkers longitudinally, we cannot comment on within-subject variability, change in marker concentration as a function of change in renal progression or the value in predicting response to therapy. Markers with this latter attribute may be useful, for instance, when personalizing specific medication use. Because our study constituted predominantly men residing in the USA, we cannot comment whether these results apply to women or other countries. Our subjects had established diabetic nephropathy, and biomarkers of progression in earlier stages of diabetic nephropathy may differ. As an example, subjects with type 2 diabetes, with an earlier stage of CKD, were found to have sTNFR1 and sTNFR2 to be strongly and independently associated with ESRD [23]. Strengths in the study include the following: (i) the subjects in the CKD cohort were well characterized for renal and cardiovascular disease; (ii) the prospective cohort represents the elderly prevalent or inhibited cannot be answered by our study.

In conclusion, the relationship of biomarkers with future progression of CKD depends on the definition of how CKD progression is defined. Nonetheless, we found that C-terminal FGF-23 and VEGF-A may be predictive of progression. These findings should be considered preliminary given the lack of validation in a separate cohort. Larger studies in diverse populations need to be performed before these biomarkers can be used in research or in the clinic.

**SUPPLEMENTARY DATA**

Supplementary data are available online at http://ndt.oxfordjournals.org.

**ACKNOWLEDGEMENT**

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**CONFLICT OF INTEREST STATEMENT**

None declared.

**REFERENCES**

Considerations of Nephrologists when Suggesting Dialysis in Elderly patients with Renal failure (CONSIDER): a discrete choice experiment

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ABSTRACT

Background. Nephrologists often face difficult decisions when recommending dialysis or non-dialysis (supportive) care for elderly patients, given the uncertainty around survival and the burden of dialysis. Discrete choice experiments (DCEs) mimic real-world decisions through simultaneous consideration of multiple variables. We aimed to determine the relative influence of patient characteristics on dialysis recommendations.

Methods. We conducted a DCE among Australasian nephrologists consisting of 12 scenarios of two patients (described in terms of age, gender, cognition, comorbidity, life expectancy, current quality of life (QOL), expected QOL with dialysis, social support, patient and family inclination). Nephrologists indicated which patient they preferred recommending dialysis for, or whether they preferred ‘neither’. Mixed logit models determined the odds of recommending dialysis over no dialysis. Trade-offs between QOL and survival were calculated.

Results. A total of 159 nephrologists participated (34% aged 40–49 years, 62% male and 69% Caucasian). All patient characteristics except gender significantly affected the likelihood of dialysis recommendation. Nephrologists were more likely to recommend dialysis for patients with preserved cognition (odds ratio [OR]: 68.3; 95% confidence interval [CI]: 33.4–140.0), lower comorbidity (OR: 2.1; 95% CI: 1.1–4.1), increased life expectancy (OR: 2.8; 95% CI: 2.1–3.7), high current QOL (OR: 2.8; 95% CI: 2.0–3.8) and positive patient and family dialysis inclination (OR: 27.5; 95% CI: 16.2–46.8 and OR: 2.0; 95% CI: 1.3–3.3, respectively). Nephrologists aged >65 were more likely (OR: 11.7; 95% CI: 1.8–77.2) to recommend dialysis. Nephrologists were willing to forgo 12 months of patient survival to avoid substantial QOL decrease with dialysis.

Conclusion. Nephrologists avoided dialysis recommendation if it was expected to considerably reduce QOL. To inform elderly patients’ dialysis decisions, systematic and longitudinal cognition and QOL evaluations are needed as well as better research into understanding patient preferences.