Spot urine protein measurements in kidney transplantation: a systematic review of diagnostic accuracy

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ABSTRACT

Background. Quantification of proteinuria (albuminuria) in renal transplant recipients is important for diagnostic and prognostic purposes. Recent guidelines have recommended quantification of proteinuria by spot protein-to-creatinine ratio (PCR) or spot albumin-to-creatinine ratio (ACR). Validity of spot measurements remains unclear in renal transplant recipients.

Methods. Systematic review of adult kidney transplant recipients. Studies that reported the diagnostic accuracy of PCR or ACR as compared with 24-h urine protein or albumin excretion in renal transplant recipients were included.

Results. The search identified 8 studies involving 1871 renal transplant recipients. The correlation of the PCR to 24-h protein ranged from 0.772 to 0.998 with a median value of 0.92. PCR sensitivity ranged from 63 to 99 (50% of sensitivities were >90%); PCR specificity varied from 73 to 99 (50% of specificities were >90%). Only one study reported the bias; percent bias ranged from 12 to 21% and accuracy (within 30%) ranged from 47 to 56% depending on the degree of proteinuria. For the ACR, percent bias ranged from 9 to 21%, and the accuracy (within 30%) ranged from 38 to 80%.

Conclusions. The data regarding diagnostic accuracy of PCR and ACR is limited. Only one report studied the absolute measures of agreement (bias and accuracy). We recommend verifying PCR and ACR measurements with a 24-h protein before making any major diagnostic (e.g. biopsy) or therapeutic (e.g. change in immunosuppressive agents) decisions in this population.

Keywords: accuracy, albuminuria, kidney transplantation, protein-to-creatinine ratio, albumin-to-creatinine ratio, proteinuria

INTRODUCTION

The collection of a 24-h urinary protein (24-UP) or 24-h urinary albumin (24-UA) is the traditional method for


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quantifying proteinuria or albuminuria [1]. For renal transplant recipients, the assessment of protein and albumin excretion can indicate early disease such as transplant glomerulopathy or recurrent glomerulonephritis [2]. However, there are several downsides to using the 24-h collection method such as patient compliance, time required, costs involved, inconvenience of handling urine for 24 h and inappropriate collection. An alternative to timed urine collection is the use of spot samples for the calculation of the protein:creatinine ratio (PCR) or the albumin:creatinine ratio (ACR) [2].

Spot samples are easily obtained and more convenient for patients. Dyson et al. [2] investigated renal transplant recipients and found that the PCR was more cost-effective and preferred by patients and staff. They also found that its predictive value for the diagnosis of proteinuria was equivalent to the 24-UP. According to the Improving Global Outcomes (KDIGO) 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease [3] and the Concise UK Chronic Kidney Disease guidelines [4], 24-h urine collection is not necessary for the confirmation of proteinuria. Instead, a PCR >45 mg/mmol or an ACR >30 mg/mmol can be the basis for the diagnosis, based on observational diagnostic accuracy studies [4]. However, the validity of spot protein measurements in the renal transplant population remains unclear. Accordingly, this review aimed to synthesize the evidence on the diagnostic accuracy of PCR and ACR compared with 24-h urine collections in renal transplant recipients.

METHODS

Eligibility criteria

This review was based on a protocol, and we followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [5]. We included published peer-reviewed studies only if they reported disaggregated diagnostic test statistics for the PCR or the ACR, with the 24-h urine collection as the reference standard in renal transplant recipients. Studies that enrolled multiple organ transplants were excluded, as well as uncontrolled studies, and partial or duplicate reports.

Search and selection

We developed and ran structured searches in MEDLINE (1948 to 28 January 2013), EMBASE (1947 to 25 January 2013) and the Cochrane Central Register of Controlled Trials (up to December 2012) in the Ovid interface (Supplementary data, Appendix 1). Search outputs were exported into Reference Manager® (version 12). Two trained reviewers (A.B. and R.D) independently screened the titles and abstracts for eligibility. Potentially eligible records were reviewed as in full text to confirm all eligibility criteria, especially regarding the inclusion of renal transplant recipients. Any disagreements were referred to a third reviewer (M.K. or G.K.). Additionally, we screened the reference lists of all reports for additional studies. There was no limitation based on publication date or language. Only data available in the published reports were used in this analysis and no attempt was made to obtain raw data from authors.

Data collection

We designed an electronic data collection form (Microsoft Excel®, 2003) and we piloted it on three studies. Two trained reviewers (A.B. and R.D.) independently reviewed each study and extracted data pertaining to identification, methods, funding and quality assessment of primary studies. Disagreements were resolved by discussion or referral to a third reviewer (M.K. or G.K.).

Analysis

Methodological quality of studies was assessed using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool [6]. The QUADAS tool has 14 items, each scored as ‘yes’, ‘no’, ‘unclear’ or ‘not applicable’. Two QUADAS items (item 7: ‘Was the reference standard independent of the index test?’ and item 12: ‘Were the same clinical data available when the test results were interpreted as would be available when the test is used in practice?’) were omitted as they were not applicable. The QUADAS tool does not provide an overall quality score and we did not create one as using different methods for weighting can lead to different scores and conclusions [7]. Heterogeneity was assessed qualitatively as well as by plotting the sensitivity and specificity (with 95% confidence limits) of the PCR for the cut point of proteinuria >1 gm/day [8]. We calculated 95% confidence intervals (95% CI) for sensitivity and specificity if it was not reported. Similarly, likelihood ratios were calculated if not provided in the original report.

RESULTS

Study selection

We identified 4167 reports, including 908 duplicates. We deemed 3035 citations not relevant to our study question leaving 224 potentially eligible reports that we retrieved and reviewed in full text. We excluded 216 reports for the following reasons: did not include renal transplant recipients (n = 162); not relevant based on eligibility criteria (n = 38); not designed as a diagnostic accuracy investigation (n = 6); no disaggregated data for the renal transplant recipients (n = 5) and did not use the reference standard or index test of interest (n = 5)(Figure 1).

Study characteristics

The eight included studies [2, 9–15] were published between 1987 and 2012 and included 1871 renal transplant recipients. Patients enrolled were exclusively renal transplant patients, except in one study [15] where they represented a sub-group. Laboratory testing was conducted 1 day to 25.2 years after renal transplantation (reported in n = 5 articles [9–11, 13, 14]). The sex distribution was reported only in four articles [9–11, 13] (57.1–79.2% males) (Table 1).

Six studies [2, 11–15] used PCR as their only index test, one study [9] used both PCR and ACR, and one study [10] used ACR alone. The reference test was most often 24-UP, but two
reports [9, 10] measured the 24-h albumin excretion. Morning collection of spot urine samples was specified in six reports [2, 9–11, 13, 14].

Data were collected prospectively in all but one study. Six studies reported cut-off values for the reference standard and seven studies reported cut-off values for the index test.

Six studies reported sensitivity or specificity but none reported a likelihood ratio or a diagnostic odds ratio. Only two studies presented positive and negative predictive values. Two studies presented a receiver operating characteristic (ROC) curve along with its area under the curve (AUC).

**Quality assessment**

The QUADAS tool items are summarized in Figure 2. Seven of the eight studies reported at least 50% of the QUADAS items. The most poorly addressed questions of the QUADAS tool were: ‘Was selection criteria clearly described’ and ‘Were uninterpretable, indeterminate or intermediate test results reported’ (Figure 2).

**Diagnostic assessment**

The correlation of the PCR to 24-UP ranged from 0.772 to 0.998 with a median value of 0.92 (Table 2). PCR sensitivity ranged from 63 to 99%; PCR specificity varied from 73 to 99%. Of the 16 different PCR sensitivities reported, 50% were ≥90% and 75% were ≥80% (Table 2). For the PCR specificities, 81% were ≥90% and 94% were ≥80% (Table 2). Only one study reported the correlation between ACR and 24-UA (r = 0.96) (Table 3). For ACR, sensitivity ranged from 79 to 100% and specificity varied from 81 to 98%. Of the 9 different ACR sensitivities reported, 56% were ≥90 and 89% were ≥80% (Table 3). For the ACR specificities, 33% were ≥90% and all were ≥80% (Table 3). Only one study\(^{23}\) reported the bias, precision and accuracy of ACR and PCR. For the PCR, percent bias ranged from 12 to 21%, and the accuracy (within 30% of 24-UP) was only 47 to 56% depending on the degree of proteinuria\(^{23}\). For the ACR, percent bias ranged from 9 to 21%, and the accuracy (within 30%) ranged from 38 to 80% depending on the degree of albuminuria\(^{23}\). The AUC ranged from 0.87 to 0.95 for PCR and 0.93–0.96 for ACR depending on the degree of proteinuria in the study by Akbari et al. [9]. The AUC for ACR was 0.94 for men and 0.98 for women in the report by Erman et al. [10].

**Meta-analysis**

We could not perform a meta-analysis as pooling of the cut-off points would require either raw data (to create a pooled ROC curve on the basis of sensitivity /specificity values per the cut-off point), or published ROC curves or the actual number of positive and negatives based on the reference standard [8]. We did not have access to raw data and only one study [2] for proteinuria and one study [10] for albuminuria had published ROC curves. More importantly, the heterogeneity of the...
We identified eight non-randomized diagnostic accuracy studies providing data on PCR and ACR in renal transplant recipients. There was more published data on the PCR and there was excellent correlation with the 24-UP in the majority of studies. For the PCR, most reported sensitivity and specificity values were greater than 80% and approximately two-thirds were above 90%. Only one study evaluated the absolute agreement (bias, precision and accuracy) of PCR and ACR with 24-UP. Our findings suggest that the cutoff values of PCR and ACR are quite variable and that the accuracy may be sub-optimal in the renal transplant population.

Proteinuria and albuminuria have been associated with progressive kidney disease, graft loss and mortality in renal transplant recipients [16–19]. In a study involving 3365 kidney transplant patients, the risk of graft loss (adjusted relative risk 2.33) and mortality (adjusted relative risk 2.05) were significantly increased for patients with >0.5 g/day of proteinuria [20]. There have been several other studies linking proteinuria with death and graft loss [17, 21–26]. In these analyses, the adjusted relative risk for allograft loss has ranged from 1.15 to 5.34 with an average value of 2.7 [27]. Similarly, the adjusted risk of death for patients with proteinuria has ranged from 1.20 to 8.60 with a median value of 1.98 [27]. Most studies have also shown a consistent association between worsening proteinuria and cardiovascular events as well as cardiovascular cause of death. Moreover, for patients with significant proteinuria (i.e. >1.5 g/day), glomerular pathology (e.g. recurrent and de novo glomerulonephritis and transplant glomerulopathy) seems most common [21]. Thus, accurate assessment of proteinuria is necessary for prognostic as well as diagnostic purposes and may be a target for therapy.

Although 24-UP is the gold standard test for quantifying proteinuria, it is cumbersome and prone to collection errors [28]. Spot urine collections are easily performed and do account for dilution of protein by correcting for urine creatinine. KDIGO transplant guidelines recommend using the ACR or PCR as an alternate to the 24-UP [3]. Our review indicates that optimal sensitivity and specificity correspond to quite different cutoff values. For example, in the study by Torng et al. [1] the optimal cutoff for PCR was 100 g/mol (sensitivity 74%, specificity 98%) for proteinuria >1 gm/day as compared with a cutoff value of 75 g/mol (sensitivity 89%, specificity 93%) in the study by Dyson et al. [2]. Thus, if a transplant recipient had a PCR of 85 g/mol, Torng et al. would classify the patient as having <1 gm/day proteinuria of whereas the data from Dyson et al. would suggest the patient had >1 gm/day proteinuria.

Most of the studies have evaluated correlation, sensitivity and specificity of PCR and ACR in relation to 24-UP. Correlation measures relative agreement while sensitivity and specificity are statistical measures of the performance of a binary classification. None of these measures gives the clinician
information about quantitative accuracy of the test. A single study in our review measured the absolute agreement between ACR and PCR to 24-UP and found it to be suboptimal [9].

The data in this current systematic review is heterogeneous. The heterogeneity is likely secondary to different populations being studied at different time points post-transplantation as well as with different laboratory methodologies. Immediately post-transplantation creatinine excretion will be elevated due to recovering kidney function. In this situation, both the PCR and ACR will be underestimated. In subsequent months when creatinine excretion declines, there may be an overestimation of the ACR and PCR [29]. In addition, it may not be appropriate to combine data from males and females given the differences in muscle mass and thus creatinine excretion. Finally, the different methodologies used to measure protein excretion may have contributed to the study heterogeneity.

Our search yielded a limited number of studies despite a broad search strategy. This included systematically verifying whether disaggregated data were reported for renal transplant patients enrolled as a sub-group within a larger sample. Others have reported on the difficulty in identifying diagnostic accuracy studies for inclusion in systematic reviews [30, 31]. Given the limited number of studies we identified in this review, it is possible that this applies to the renal

FIGURE 2: Assessment of methodological quality (QUADAS tool).
### Table 2. Reported cut-off points and diagnostic accuracy statistics for 24-h UP and PCR in kidney transplant recipients

<table>
<thead>
<tr>
<th>First author and year</th>
<th>24-h UP</th>
<th>PCR (g/mol)</th>
<th>Specificity % (95% CI)</th>
<th>Sensitivity % (95% CI)</th>
<th>Positive likelihood ratio</th>
<th>Negative likelihood ratio</th>
<th>Correlation coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Krishna [11]</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>0.998</td>
</tr>
<tr>
<td>Villafruela [15]</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>0.943</td>
</tr>
<tr>
<td>Dyson [2]</td>
<td>&gt;0.5 g/24 h</td>
<td>40</td>
<td>73 (69.0, 77.0)</td>
<td>83 (79.6, 86.4)</td>
<td>4.3</td>
<td>0.33</td>
<td>0.772</td>
</tr>
<tr>
<td></td>
<td>&gt;1.0 g/24 h</td>
<td>75</td>
<td>93 (90.7, 95.3)</td>
<td>89 (86.2, 91.8)</td>
<td>8.5</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;2.0 g/24 h</td>
<td>90</td>
<td>91 (88.4, 93.6)</td>
<td>92 (89.5, 94.5)</td>
<td>11.4</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>Steinhauslin [13]</td>
<td>&gt;0.25 g/24 h/1.73 m²</td>
<td>22</td>
<td>91 (88.5, 93.5)</td>
<td>93 (90.8, 95.2)</td>
<td>13</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;1.0 g/24 h/1.73 m²</td>
<td>84</td>
<td>94 (92.0, 96.0)</td>
<td>97 (95.5, 98.5)</td>
<td>31.3</td>
<td>0.06</td>
<td>0.93</td>
</tr>
<tr>
<td></td>
<td>&gt;2.0 g/24 h/1.73 m²</td>
<td>190</td>
<td>94 (92.0, 96.0)</td>
<td>97 (95.5, 98.5)</td>
<td>31.3</td>
<td>0.06</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;3.5 g/24 h/1.73 m²</td>
<td>300</td>
<td>94 (92.0, 96.0)</td>
<td>99 (98.1, 99.9)</td>
<td>94</td>
<td>0.06</td>
<td></td>
</tr>
<tr>
<td>Torng [14]</td>
<td>&gt;0.25 g/24 h/1.73 m²</td>
<td>40</td>
<td>94 (91.3, 96.7)</td>
<td>85 (89.0, 90.9)</td>
<td>6.3</td>
<td>0.07</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;1.0 g/24 h/1.73 m²</td>
<td>100</td>
<td>98 (96.4, 99.6)</td>
<td>74 (68.9, 79.1)</td>
<td>3.8</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;2.0 g/24 h/1.73 m²</td>
<td>200</td>
<td>93 (90.1, 95.9)</td>
<td>90 (86.5, 93.5)</td>
<td>9.3</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;3.5 g/24 h/1.73 m²</td>
<td>300</td>
<td>98 (96.4, 99.6)</td>
<td>63 (57.4, 68.6)</td>
<td>2.7</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>Rodrigo [12]</td>
<td>&lt;0.15 g/24 h</td>
<td>17</td>
<td>97 (96.6, 97.4)</td>
<td>96 (95.6, 96.4)</td>
<td>2.9</td>
<td>0.05</td>
<td>0.921</td>
</tr>
<tr>
<td></td>
<td>&gt;3 g/24 h</td>
<td>339</td>
<td>99 (98.8, 99.2)</td>
<td>73 (72.0, 74.0)</td>
<td>3.7</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Akbari [9]</td>
<td>&gt;0.15 g/24 h/1.73 m²</td>
<td>19</td>
<td>87 (78, 93)</td>
<td>74 (65, 82)</td>
<td>3.4</td>
<td>0.18</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;0.3 g/24 h/1.73 m²</td>
<td>26</td>
<td>89 (82, 93)</td>
<td>86 (74, 93)</td>
<td>6.4</td>
<td>0.13</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥1.0 g/24 h/1.73 m²</td>
<td>84</td>
<td>98 (95, 100)</td>
<td>94 (71, 99)</td>
<td>16.3</td>
<td>0.02</td>
<td></td>
</tr>
</tbody>
</table>

To convert g/mol to mg/g multiply by 0.113. NR: not reported; PCR: protein to creatinine ratio.

### Table 3. Reported cut-off points and diagnostic accuracy statistics for 24-h UA and ACR in kidney transplant recipients

<table>
<thead>
<tr>
<th>First author and year</th>
<th>24-h UA</th>
<th>ACR (g/mol)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Positive likelihood ratio</th>
<th>Negative likelihood ratio</th>
<th>Correlation coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erman [10]</td>
<td>≥30 mg/24 h</td>
<td>&gt;1.9</td>
<td>89 (84.3, 93.7)</td>
<td>81 (75.1, 86.9)</td>
<td>4.7</td>
<td>0.14</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Males</td>
<td>&gt;2.4</td>
<td>87 (81.9, 92.2)</td>
<td>89 (84.3, 93.7)</td>
<td>7.9</td>
<td>0.15</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;3.4</td>
<td>79 (72.8, 85.2)</td>
<td>95 (91.7, 98.3)</td>
<td>15.8</td>
<td>0.22</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Females</td>
<td>&gt;2.7</td>
<td>100 (100, 100)</td>
<td>88 (80.6, 95.5)</td>
<td>8.3</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;2.8</td>
<td>97 (93.1, 100)</td>
<td>88 (80.6, 95.5)</td>
<td>8.08</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;3.4</td>
<td>90 (83.1, 96.9)</td>
<td>88 (80.6, 95.5)</td>
<td>7.5</td>
<td>0.11</td>
<td></td>
</tr>
<tr>
<td>Akbari [9]</td>
<td>≥30 mg/24 h/1.73 m²</td>
<td>≥2.7</td>
<td>87 (79.0, 93.0)</td>
<td>87 (79.0, 93.0)</td>
<td>6.7</td>
<td>0.15</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;300 mg/24 h/1.73 m²</td>
<td>&gt;19.8</td>
<td>96 (78.0, 99.0)</td>
<td>96 (78.0, 99.0)</td>
<td>24</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥1000 mg/24 h/1.73 m²</td>
<td>≥65.8</td>
<td>90 (56.0, 98.0)</td>
<td>90 (56.0, 98.0)</td>
<td>9</td>
<td>0.11</td>
<td>0.96</td>
</tr>
</tbody>
</table>

To convert g/mol to mg/g multiply by 0.113. NR: not reported; ACR: Albumin to creatinine ratio.
transplantation literature as well. Unfortunately, the quality of reporting was quite poor. The authors did not typically report how the study setting was identified, how patient sampling was performed, whether the same reference standard was used on all patients, and whether there were any uninterpretable results [32]. Lijmer et al. [33] have shown that diagnostic accuracy studies of lower methodological quality tend to overestimate the diagnostic performance of a test. Thus, the results in terms of diagnostic accuracy for PCR and ACR in this review may in fact be more favorable than the ‘true value’.

In conclusion, although the ACR and PCR are routinely used in kidney transplant recipients, the data regarding diagnostic accuracy is of limited utility to the practicing clinician. While the data to date have shown acceptable correlation, sensitivity and specificity, these measures are not useful when trying to determine how much proteinuria or albuminuria is truly present. Further research is needed to better clarify absolute measures of agreement (e.g. bias and accuracy) between the 24-UP and the PCR/ACR in renal transplant recipients. In addition studies should report sensitivity and specificity of ACR and PCR at clinically used cut-off points. Separate analysis of data should be performed in females and males. Moreover, studies should be powered for outcomes. Until these data are available, we recommend verifying PCR and ACR measurements with a 24-UP before making major diagnostic (e.g. biopsy) or therapeutic (e.g. change in immunosuppressive agent) decisions in this population.

SUPPLEMENTARY DATA

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

Background. New-onset diabetes after transplantation (NODAT) is a common complication after renal transplantation. There are limited available oral drugs to treat hyperglycaemia in this population owing to reduced renal function, potential interactions with immunosuppressive drugs and adverse effects such as hypoglycaemic events that may increase the cardiovascular risk. This study was initiated to investigate efficacy and safety of sitagliptin treatment that may represent a novel alternative in renal transplant recipients.

Methods. Nineteen long-term stable renal transplant recipients with NODAT were included in a controlled, cross-over trial of sitagliptin treatment in renal transplant recipients.

Short-term efficacy and safety of sitagliptin treatment in long-term stable renal recipients with new-onset diabetes after transplantation

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