Developing a self-administered CKD symptom assessment instrument

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Abstract

Background. Current disease-centred therapies for CKD focus on preserving the GFR but often ignore patient-reported symptoms. This purpose of this report is to describe the development of an instrument to measure the presence and severity of a wide range of symptoms commonly attributable to CKD.

Methods. A 37-item questionnaire was administered along with the Kidney Disease Quality of Life instrument to 92 patients with CKD not on dialysis (24% black, 5% women, mean age 68 years, 68% with diabetes mellitus). To discover groups of symptoms, agglomerative cluster analysis followed by exploratory common factor analysis was performed. Construct validity, internal reliability, convergent and discriminant validity, test–retest reliability and finally the association of various symptom domains with objective measurements such as estimated GFR and haemoglobin were tested.

Results. The top five symptoms of at least moderate severity in decreasing order of prevalence were ‘tire easily’, limited physical activity, nocturia, joint pain and ‘stop and rest often’. Four common factors emerged that could be broadly classified into neuropsychiatric, cardiovascular, uraemia and anaemia symptoms accounting for 73% of the total variance in the sample. The coefficient alpha for each of these factors approached 0.9. The test–retest reliability in 41 patients over 8 weeks was likewise high. There was good convergent and divergent validity. However, there was little relationship between estimated GFR and symptom scores.

Conclusions. The assessment of symptom burden among patients with CKD may be facilitated by incorporating this instrument in routine practice and clinical trials.

Keywords: chronic kidney disease; cluster analysis; factor analysis; questionnaire; symptom

Introduction

Chronic kidney disease (CKD) is a leading worldwide cause of morbidity and mortality and is associated with substantial impairment in physical and mental health [1,2]. Current disease-centred therapies geared towards preservation of glomerular filtration rate (GFR) and reducing proteinuria fail to measure amelioration of symptoms, which is an important factor for our patients [3,4]. Patient-reported symptoms can detect differences between patients and within patients over time. More importantly, as new therapies are tested in the future it will be critically important to assess their effects on patient-reported symptoms and health ratings.

Although many clinicians recognize the appearance of symptoms attributable to uraemia, somewhat surprisingly, few studies have sought the relationship of CKD stage and symptoms attributable to kidney disease. A recent study reported that patients with advanced CKD not on dialysis have a high symptom burden but this symptom burden bore no relationship to GFR [5]. A large multicentre study found no relationship of GFR with health-related quality of life domains [6]. Another study reported that proteinuria but not GFR affected patient-reported health-related quality of life as measured by the Kidney Disease Quality of Life (KDQOL) instrument [7]. Thus, existing evidence provides poor relationship between GFR and quality of life or symptom burden in patients with CKD.

The KDQOL instrument was developed for evaluating quality of life in patients on dialysis [8,9]; this instrument often does not capture the gamut of symptoms that may be relevant and bothersome to patients with CKD not yet on dialysis. For example, patients with CKD often complain of nocturia, pedal oedema, change in taste of food, feeling cold or having restless legs—symptoms that may be related to myocardial dysfunction, impaired glomerular filtration barrier, accumulation of uraemic toxins, anaemia or iron deficiency [1,10,11]. Murtagh et al. reviewed the literature on the prevalence of symptoms in patients with CKD [3]. Of the 59 studies identified, none were performed in patients not on dialysis and only 11 focused at capturing the full range of symptoms experienced by patients with end-stage renal disease. Thus, there exists a need to develop a disease-specific instrument that accurately measures symptoms of CKD patients.

This report describes development of an instrument to measure the presence and severity of various symptoms commonly attributable to kidney disease. To validate this
instrument for use in patients with CKD not treated with dialysis, we tested the construct validity, internal reliability, convergent and discriminant validity, test–retest reliability and finally the association of various symptom domains with objective measurements such as estimated GFR and haemoglobin.

Methods

The study was approved by the institutional review board and all subjects gave written informed consent.

Participants

Patients with CKD attending the renal clinics of an inner-city county hospital and a Department of Veterans Affairs medical centre in Indianapolis were recruited between May 2008 and January 2009. To be eligible, patients had to have an estimated GFR of between 15 and 60 mL/min/1.73 m² or have clinically significant proteinuria.

Development of the questionnaire

Seven patients who were under the care of the author for many years and believed to have insight into their disease were interviewed using open-ended questions to ascertain the most bothersome aspects of their kidney disease. From these interviews and a review of the literature, a questionnaire that assessed both mental (e.g. cognition, depression, anxiety, social interaction) and physical (e.g. symptoms of anaemia or uraemia or heart failure) domains of health was developed. The questionnaire was self-administered along with Kidney Disease Quality of Life Questionnaire (KDQOL) at the same visit. A subset of patients had the measurement repeated within 8 weeks of the first visit.

Data analysis

To explore the grouping of symptoms, A cluster analysis was first performed on a 37-item questionnaire administered to 92 patients. Dissimilarity between symptoms was measured by Euclidean distance and average linkage agglomerative cluster analysis was used to evaluate the grouping of symptoms [12]. A dendrogram was created to demonstrate the hierarchical relationship between symptoms. Exploratory factor analysis was then performed on the original 37-item questionnaire. A correlation matrix was calculated, and factors were extracted by common factor analysis. Eigenvalue was required to be at least 1 for the factor to be retained and used Kaiser–Meyer–Olkin (KMO) measure of sampling adequacy to quantify the goodness-of-fit of the principal factor model [13]. Eigenvalue of a factor indicates how much variance of the scree plot. A varimax rotation was used. Items in each scale must account for and this was used in conjunction with examination of the grouping of symptoms among patients. The height of symptoms joining the tree at high points underscoring the high comorbidity in this population. Convergent validity was established by examining the interrelations of the newly created symptom scores with KDQOL using complete linkage analysis. KDQOL is a kidney disease-specific health-related quality of life questionnaire with 18 subscales and 2 composite scales of physical and mental health [8]. Convergent validity was also established using objective measurements such as seeking the relationship of haemoglobin with anaemia subscale, estimated GFR with the uraemia subscale and history of heart failure with cardiovascular subscale. Divergent validity was established by measuring the grouping of symptoms among patients. The height of the vertical lines and the range of the dissimilarity axis give visual clues about the strength of clustering. Symptoms are more related when closer on the x-axis and having a low loadings on other factors. Cronbach’s alpha was calculated as a measure of reliability reflecting the average correlation among all items in a scale also known as internal consistency.

Symptoms in the newly created scales were summed and scored from 0 to 100. For example, in a three-item scale, the sum of symptom scores could vary from 3 to 15. So 3 was subtracted from the sum of symptoms and then multiplied by 100/12 to give a score that ranged from 0 (no symptoms) to 100 (most symptomatic). If dual factor loadings were present for an item, the item was retained in each scale.

Table 1. Clinical and demographic characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean or n</th>
<th>SD or %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>67.5</td>
<td>11.0</td>
</tr>
<tr>
<td>Male</td>
<td>87</td>
<td>95%</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>97.7</td>
<td>23.9</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>32.4</td>
<td>7.2</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>67</td>
<td>73%</td>
</tr>
<tr>
<td>African American</td>
<td>22</td>
<td>24%</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
<td>3%</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>63</td>
<td>68%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>88</td>
<td>90%</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>31</td>
<td>34%</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>19</td>
<td>21%</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>21</td>
<td>23%</td>
</tr>
<tr>
<td>Stroke</td>
<td>19</td>
<td>21%</td>
</tr>
<tr>
<td>Pedal oedema</td>
<td>60</td>
<td>65%</td>
</tr>
<tr>
<td>Tobacco use</td>
<td>20</td>
<td>22%</td>
</tr>
<tr>
<td>Alcohol use</td>
<td>40</td>
<td>43%</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>2.3</td>
<td>1.0</td>
</tr>
<tr>
<td>Estimated GFR (mL/min/1.73 m²)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;0.22</td>
<td>5</td>
<td>5%</td>
</tr>
<tr>
<td>0.22 to &lt;1</td>
<td>19</td>
<td>21%</td>
</tr>
<tr>
<td>1 to &lt;3</td>
<td>31</td>
<td>34%</td>
</tr>
<tr>
<td>3 or more</td>
<td>37</td>
<td>40%</td>
</tr>
<tr>
<td>Proteinuria (pr/ct ratio)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;0.22</td>
<td>42</td>
<td>46%</td>
</tr>
<tr>
<td>0.22 to &lt;1</td>
<td>21</td>
<td>23%</td>
</tr>
<tr>
<td>1 to &lt;3</td>
<td>21</td>
<td>23%</td>
</tr>
<tr>
<td>3 or more</td>
<td>8</td>
<td>9%</td>
</tr>
<tr>
<td>Serum albumin (g/dL)</td>
<td>4.1</td>
<td>0.4</td>
</tr>
<tr>
<td>Haemoglobin (g/dL)</td>
<td>12.2</td>
<td>1.6</td>
</tr>
</tbody>
</table>

The demographic and clinical characteristics of the 92 patients with CKD, none treated with dialysis, are shown in Table 1. There were mostly men; 60% of the patients had eGFR of <60 mL/min/1.73 m² and 54% had significant proteinuria. The estimated GFRs are shown in Table 1. Two-thirds of the patients were being treated for diabetes mellitus and 21% had a history of congestive heart failure underscoring the high comorbidity in this population.

The frequency distribution of symptoms and their severity over the prior 4 weeks is shown in Table 2. The frequency distribution of item response-options was skewed towards better health for symptoms such as diarrhoea, appetite and taste and skewed towards worse health for symptoms such as nocturia, joint pains, cramping and numbness. Interitem correlation coefficients were all <0.75 in every instance. Figure 1 shows a dendrogram that graphically represents the grouping of symptoms among patients. The height of the vertical lines and the range of the dissimilarity axis give visual clues about the strength of clustering. Symptoms are more related when closer on the x-axis and having a low loadings on other factors. Cronbach’s alpha was calculated as a measure of reliability reflecting the average correlation among all items in a scale also known as internal consistency.
other symptoms. Broadly speaking, two clusters of symptoms are readily apparent; those of the left representing the physical domain whereas those on the right the mental domain. The first 10 symptoms in the physical domain (from tiredness to cramp) appear to reflect cardiovascular deconditioning and the remaining symptoms that of anaemia. The first 10 symptoms (from difficulty concentrating to uncertain future) appear to reflect neuropsychiatric symptoms and symptoms from appetite to bad taste that of uraemia. These relationships were explored further with factor analysis.

Using common factor analysis, six factors emerged each with Eigenvalue of >1 when all 37 symptoms were analysed. However, the last two factors had <3 items with loading of >0.4. Therefore, a four-factor solution was deemed more relevant as prespecified. These symptoms and their loadings to the common factors are shown in Table 3. These factors could be broadly classified into neuropsychiatric, cardiovascular, uraemia and anaemia. The common factors together accounted for 73% of the total variance in the sample. The coefficient alpha for each of these factors approached 0.9 and the overall measure of sampling adequacy was between 0.8 and 0.89, which is considered ‘meritorious’ by the traditional criteria [13].

Individual scores of each of these four factors were scaled from 0 to 100 (worst to best). The relationship of neuropsychiatric score regressed on mental health composite score of the KDQOL instrument yielded $r^2$ of 0.41 and $P < 0.001$ (Figure 2). There was a statistically significant relationship between haemoglobin and anaemia score. Those with a history of congestive heart failure fared worse compared to those without ($P = 0.015$, Kruskal–Wallis test). However, there was no relationship seen between putative uraemia score and estimated GFR.

Figure 3 shows the dendrogram of (dis)similarity between 18 subdomains of KDQOL, the 2 composite scores and the newly created scale (in capitals). Uraemia score was related most closely to ‘kidney disease burden’ scale of KDQOL. Neuropsychiatric score was closely related to sleep, overall health and pain. Clustering was noted between physical function, cardiovascular score and anaemia score. These data demonstrate the convergent validity of the newly created scores.

Forty-one patients completed an average of 2.5 questionnaires over an 8-week period yielding 107 completed questionnaires. The test–retest reliability measured by intraclass correlation coefficient for neuropsychiatric subscale was 0.805 (95% CI 0.705–0.905), the cardiovascular scale

### Table 2. Symptom prevalence over the previous 4 weeks

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Mean</th>
<th>SD</th>
<th>Skew</th>
<th>Strongly agree</th>
<th>Moderately agree</th>
<th>Neither agree nor disagree</th>
<th>Moderately disagree</th>
<th>Strongly disagree</th>
<th>Missing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tire easily</td>
<td>2.0</td>
<td>1.1</td>
<td>1.06</td>
<td>40%</td>
<td>36%</td>
<td>12%</td>
<td>9%</td>
<td>3%</td>
<td>0%</td>
</tr>
<tr>
<td>Stop and rest often</td>
<td>2.4</td>
<td>1.3</td>
<td>0.68</td>
<td>27%</td>
<td>35%</td>
<td>16%</td>
<td>11%</td>
<td>11%</td>
<td>0%</td>
</tr>
<tr>
<td>Limited physical activities</td>
<td>2.2</td>
<td>1.3</td>
<td>0.97</td>
<td>37%</td>
<td>33%</td>
<td>12%</td>
<td>7%</td>
<td>11%</td>
<td>1%</td>
</tr>
<tr>
<td>Difficulty concentrating</td>
<td>3.2</td>
<td>1.2</td>
<td>0.07</td>
<td>4%</td>
<td>29%</td>
<td>24%</td>
<td>23%</td>
<td>20%</td>
<td>0%</td>
</tr>
<tr>
<td>Lost interest in things</td>
<td>3.2</td>
<td>1.2</td>
<td>−0.02</td>
<td>7%</td>
<td>27%</td>
<td>23%</td>
<td>24%</td>
<td>20%</td>
<td>0%</td>
</tr>
<tr>
<td>Not interested in other people</td>
<td>3.8</td>
<td>1.1</td>
<td>−0.44</td>
<td>1%</td>
<td>16%</td>
<td>21%</td>
<td>28%</td>
<td>34%</td>
<td>0%</td>
</tr>
<tr>
<td>Not well rested</td>
<td>2.8</td>
<td>1.3</td>
<td>0.19</td>
<td>18%</td>
<td>28%</td>
<td>21%</td>
<td>22%</td>
<td>11%</td>
<td>0%</td>
</tr>
<tr>
<td>Fall asleep during the day</td>
<td>2.7</td>
<td>1.3</td>
<td>0.39</td>
<td>20%</td>
<td>34%</td>
<td>16%</td>
<td>14%</td>
<td>14%</td>
<td>0%</td>
</tr>
<tr>
<td>Urge to sleep more</td>
<td>2.5</td>
<td>1.3</td>
<td>0.58</td>
<td>22%</td>
<td>36%</td>
<td>20%</td>
<td>12%</td>
<td>11%</td>
<td>0%</td>
</tr>
<tr>
<td>Irritable</td>
<td>3.3</td>
<td>1.3</td>
<td>−0.02</td>
<td>7%</td>
<td>26%</td>
<td>24%</td>
<td>20%</td>
<td>24%</td>
<td>0%</td>
</tr>
<tr>
<td>Impatient with others</td>
<td>3.2</td>
<td>1.2</td>
<td>0.04</td>
<td>8%</td>
<td>24%</td>
<td>30%</td>
<td>18%</td>
<td>20%</td>
<td>0%</td>
</tr>
<tr>
<td>My personality has changed</td>
<td>3.3</td>
<td>1.3</td>
<td>−0.11</td>
<td>9%</td>
<td>20%</td>
<td>29%</td>
<td>13%</td>
<td>29%</td>
<td>0%</td>
</tr>
<tr>
<td>I am not the same person</td>
<td>3.0</td>
<td>1.3</td>
<td>0.11</td>
<td>15%</td>
<td>24%</td>
<td>27%</td>
<td>17%</td>
<td>16%</td>
<td>0%</td>
</tr>
<tr>
<td>Discouraged about the future</td>
<td>3.2</td>
<td>1.4</td>
<td>−0.17</td>
<td>16%</td>
<td>18%</td>
<td>20%</td>
<td>24%</td>
<td>22%</td>
<td>0%</td>
</tr>
<tr>
<td>Withdrawn from others</td>
<td>3.5</td>
<td>1.2</td>
<td>−0.18</td>
<td>3%</td>
<td>20%</td>
<td>27%</td>
<td>21%</td>
<td>28%</td>
<td>1%</td>
</tr>
<tr>
<td>Lost confidence in myself</td>
<td>3.7</td>
<td>1.3</td>
<td>−0.55</td>
<td>5%</td>
<td>14%</td>
<td>21%</td>
<td>23%</td>
<td>36%</td>
<td>1%</td>
</tr>
<tr>
<td>Difficulty breathing</td>
<td>3.3</td>
<td>1.3</td>
<td>−0.24</td>
<td>11%</td>
<td>22%</td>
<td>17%</td>
<td>26%</td>
<td>24%</td>
<td>0%</td>
</tr>
<tr>
<td>Bone pain</td>
<td>3.3</td>
<td>1.4</td>
<td>−0.13</td>
<td>11%</td>
<td>26%</td>
<td>15%</td>
<td>17%</td>
<td>30%</td>
<td>0%</td>
</tr>
<tr>
<td>Loss of appetite</td>
<td>3.7</td>
<td>1.3</td>
<td>−0.62</td>
<td>7%</td>
<td>12%</td>
<td>22%</td>
<td>22%</td>
<td>23%</td>
<td>0%</td>
</tr>
<tr>
<td>Poor quality of sleep</td>
<td>2.8</td>
<td>1.4</td>
<td>0.30</td>
<td>22%</td>
<td>29%</td>
<td>15%</td>
<td>16%</td>
<td>17%</td>
<td>0%</td>
</tr>
<tr>
<td>Loss of taste for food</td>
<td>3.6</td>
<td>1.4</td>
<td>−0.51</td>
<td>8%</td>
<td>21%</td>
<td>12%</td>
<td>20%</td>
<td>40%</td>
<td>0%</td>
</tr>
<tr>
<td>Feel colder than others</td>
<td>2.9</td>
<td>1.5</td>
<td>0.25</td>
<td>21%</td>
<td>27%</td>
<td>18%</td>
<td>15%</td>
<td>23%</td>
<td>0%</td>
</tr>
<tr>
<td>Sick feeling in my stomach</td>
<td>3.5</td>
<td>1.3</td>
<td>−0.34</td>
<td>5%</td>
<td>20%</td>
<td>21%</td>
<td>25%</td>
<td>29%</td>
<td>0%</td>
</tr>
<tr>
<td>Swelling of my feet</td>
<td>2.7</td>
<td>1.4</td>
<td>0.37</td>
<td>22%</td>
<td>32%</td>
<td>15%</td>
<td>16%</td>
<td>15%</td>
<td>0%</td>
</tr>
<tr>
<td>Puffiness around face</td>
<td>3.6</td>
<td>1.2</td>
<td>−0.38</td>
<td>7%</td>
<td>14%</td>
<td>27%</td>
<td>22%</td>
<td>30%</td>
<td>0%</td>
</tr>
<tr>
<td>Easily bruise skin</td>
<td>3.0</td>
<td>1.4</td>
<td>−0.06</td>
<td>20%</td>
<td>18%</td>
<td>21%</td>
<td>23%</td>
<td>18%</td>
<td>0%</td>
</tr>
<tr>
<td>Restless legs at night</td>
<td>2.9</td>
<td>1.5</td>
<td>0.15</td>
<td>22%</td>
<td>24%</td>
<td>17%</td>
<td>15%</td>
<td>22%</td>
<td>0%</td>
</tr>
<tr>
<td>Need to pass urine at night</td>
<td>2.4</td>
<td>1.3</td>
<td>0.61</td>
<td>29%</td>
<td>34%</td>
<td>12%</td>
<td>16%</td>
<td>9%</td>
<td>0%</td>
</tr>
<tr>
<td>Dry skin</td>
<td>2.7</td>
<td>1.3</td>
<td>0.42</td>
<td>17%</td>
<td>34%</td>
<td>20%</td>
<td>14%</td>
<td>13%</td>
<td>2%</td>
</tr>
<tr>
<td>Itchy skin</td>
<td>2.7</td>
<td>1.4</td>
<td>0.37</td>
<td>24%</td>
<td>28%</td>
<td>16%</td>
<td>14%</td>
<td>16%</td>
<td>1%</td>
</tr>
<tr>
<td>Change in skin colour</td>
<td>3.3</td>
<td>1.3</td>
<td>−0.14</td>
<td>11%</td>
<td>16%</td>
<td>30%</td>
<td>16%</td>
<td>24%</td>
<td>2%</td>
</tr>
<tr>
<td>Joint pain</td>
<td>2.5</td>
<td>1.4</td>
<td>0.67</td>
<td>29%</td>
<td>33%</td>
<td>13%</td>
<td>10%</td>
<td>14%</td>
<td>1%</td>
</tr>
<tr>
<td>Muscle cramps</td>
<td>2.6</td>
<td>1.3</td>
<td>0.53</td>
<td>22%</td>
<td>36%</td>
<td>14%</td>
<td>14%</td>
<td>13%</td>
<td>1%</td>
</tr>
<tr>
<td>Numbness in toes and feet</td>
<td>2.6</td>
<td>1.3</td>
<td>0.43</td>
<td>26%</td>
<td>25%</td>
<td>23%</td>
<td>12%</td>
<td>12%</td>
<td>2%</td>
</tr>
<tr>
<td>Bad taste in mouth</td>
<td>3.4</td>
<td>1.4</td>
<td>−0.25</td>
<td>10%</td>
<td>22%</td>
<td>17%</td>
<td>20%</td>
<td>30%</td>
<td>1%</td>
</tr>
<tr>
<td>Difficult bowel movements</td>
<td>3.3</td>
<td>1.4</td>
<td>−0.17</td>
<td>12%</td>
<td>21%</td>
<td>21%</td>
<td>17%</td>
<td>28%</td>
<td>1%</td>
</tr>
<tr>
<td>Frequent bowel movements</td>
<td>3.7</td>
<td>1.2</td>
<td>−0.55</td>
<td>7%</td>
<td>11%</td>
<td>25%</td>
<td>23%</td>
<td>34%</td>
<td>1%</td>
</tr>
</tbody>
</table>
Fig. 1. Dendrogram of (dis)similarity between symptoms experienced by patients with CKD not on dialysis. Dendrogram was generated using average linkage cluster analysis. See the text for details.

Fig. 2. Divergent validity of symptom subscales. The relationships of various subscales with either other validated scales or objective measures. Neuropsychiatric score regressed on mental health composite score of the KDQOL instrument yielded $r^2$ of 0.41 and $P < 0.001$. Likewise, there was a statistically significant relationship between haemoglobin and anaemia score. Those with a history of congestive heart failure had lower scores compared to those without ($P = 0.015$, Kruskal–Wallis test). No relationship was seen between uraemia score and estimated GFR.
Table 3. Common factors and item loadings

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Neuropsychiatric</th>
<th>Cardiovascular</th>
<th>Uraemia</th>
<th>Anaemia</th>
<th>Communality</th>
<th>KMO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irritable</td>
<td>0.789</td>
<td></td>
<td></td>
<td></td>
<td>0.67</td>
<td>0.830</td>
</tr>
<tr>
<td>Withdrawn from others</td>
<td>0.745</td>
<td></td>
<td></td>
<td></td>
<td>0.70</td>
<td>0.793</td>
</tr>
<tr>
<td>Impatient with others</td>
<td>0.714</td>
<td></td>
<td></td>
<td></td>
<td>0.56</td>
<td>0.848</td>
</tr>
<tr>
<td>Lost confidence in myself</td>
<td>0.711</td>
<td></td>
<td></td>
<td></td>
<td>0.57</td>
<td>0.834</td>
</tr>
<tr>
<td>Difficulty concentrating</td>
<td>0.685</td>
<td></td>
<td></td>
<td></td>
<td>0.67</td>
<td>0.888</td>
</tr>
<tr>
<td>Lost interest in things</td>
<td>0.676</td>
<td></td>
<td></td>
<td></td>
<td>0.63</td>
<td>0.846</td>
</tr>
<tr>
<td>My personality has changed</td>
<td>0.674</td>
<td></td>
<td></td>
<td></td>
<td>0.63</td>
<td>0.867</td>
</tr>
<tr>
<td>Not interested in other people</td>
<td>0.662</td>
<td></td>
<td></td>
<td></td>
<td>0.51</td>
<td>0.868</td>
</tr>
<tr>
<td>Discouraged about the future</td>
<td>0.656</td>
<td></td>
<td></td>
<td></td>
<td>0.58</td>
<td>0.811</td>
</tr>
<tr>
<td>I am not the same person</td>
<td>0.642</td>
<td></td>
<td></td>
<td></td>
<td>0.56</td>
<td>0.864</td>
</tr>
<tr>
<td>Frequent bowel movements</td>
<td>0.409</td>
<td></td>
<td></td>
<td></td>
<td>0.40</td>
<td>0.892</td>
</tr>
<tr>
<td>Limited physical activities</td>
<td></td>
<td>0.647</td>
<td></td>
<td></td>
<td>0.53</td>
<td>0.838</td>
</tr>
<tr>
<td>Fall asleep during the day</td>
<td></td>
<td>0.617</td>
<td></td>
<td></td>
<td>0.52</td>
<td>0.850</td>
</tr>
<tr>
<td>Tire easily</td>
<td></td>
<td>0.600</td>
<td></td>
<td></td>
<td>0.48</td>
<td>0.912</td>
</tr>
<tr>
<td>Joint pain</td>
<td></td>
<td>0.571</td>
<td></td>
<td></td>
<td>0.49</td>
<td>0.767</td>
</tr>
<tr>
<td>Need to pass urine at night</td>
<td></td>
<td>0.561</td>
<td></td>
<td></td>
<td>0.50</td>
<td>0.844</td>
</tr>
<tr>
<td>Muscle cramps</td>
<td></td>
<td>0.540</td>
<td></td>
<td></td>
<td>0.49</td>
<td>0.852</td>
</tr>
<tr>
<td>Urge to sleep more</td>
<td></td>
<td>0.524</td>
<td></td>
<td></td>
<td>0.51</td>
<td>0.868</td>
</tr>
<tr>
<td>Easily bruise skin</td>
<td></td>
<td>0.506</td>
<td></td>
<td></td>
<td>0.43</td>
<td>0.846</td>
</tr>
<tr>
<td>Poor quality of sleep</td>
<td>0.462</td>
<td>0.457</td>
<td></td>
<td></td>
<td>0.55</td>
<td>0.800</td>
</tr>
<tr>
<td>Not well rested</td>
<td>0.468</td>
<td>0.441</td>
<td></td>
<td></td>
<td>0.44</td>
<td>0.796</td>
</tr>
<tr>
<td>Difficulty breathing</td>
<td></td>
<td>0.423</td>
<td></td>
<td></td>
<td>0.46</td>
<td>0.848</td>
</tr>
<tr>
<td>Swelling of my feet</td>
<td></td>
<td>0.407</td>
<td></td>
<td></td>
<td>0.35</td>
<td>0.659</td>
</tr>
<tr>
<td>Feel colder than others</td>
<td></td>
<td>0.401</td>
<td></td>
<td></td>
<td>0.37</td>
<td>0.866</td>
</tr>
<tr>
<td>Loss of appetite</td>
<td></td>
<td>0.805</td>
<td></td>
<td></td>
<td>0.77</td>
<td>0.776</td>
</tr>
<tr>
<td>Sick feeling in my stomach</td>
<td></td>
<td>0.786</td>
<td></td>
<td></td>
<td>0.71</td>
<td>0.863</td>
</tr>
<tr>
<td>Loss of taste for food</td>
<td></td>
<td>0.700</td>
<td></td>
<td></td>
<td>0.72</td>
<td>0.837</td>
</tr>
<tr>
<td>Bone Pain</td>
<td></td>
<td>0.586</td>
<td></td>
<td></td>
<td>0.57</td>
<td>0.789</td>
</tr>
<tr>
<td>Puffiness around face</td>
<td></td>
<td>0.540</td>
<td></td>
<td></td>
<td>0.51</td>
<td>0.849</td>
</tr>
<tr>
<td>Itchy skin</td>
<td></td>
<td>0.736</td>
<td></td>
<td></td>
<td>0.64</td>
<td>0.790</td>
</tr>
<tr>
<td>Dry skin</td>
<td></td>
<td>0.637</td>
<td></td>
<td></td>
<td>0.56</td>
<td>0.783</td>
</tr>
<tr>
<td>Numbness in toes and feet</td>
<td></td>
<td>0.628</td>
<td></td>
<td></td>
<td>0.48</td>
<td>0.871</td>
</tr>
<tr>
<td>Change in skin colour</td>
<td></td>
<td>0.628</td>
<td></td>
<td></td>
<td>0.56</td>
<td>0.863</td>
</tr>
<tr>
<td>Difficult bowel movements</td>
<td></td>
<td>0.570</td>
<td></td>
<td></td>
<td>0.40</td>
<td>0.756</td>
</tr>
<tr>
<td>Bad taste in mouth</td>
<td></td>
<td>0.515</td>
<td></td>
<td></td>
<td>0.539</td>
<td>0.64</td>
</tr>
<tr>
<td>Restless legs at night</td>
<td>0.428</td>
<td></td>
<td></td>
<td></td>
<td>0.462</td>
<td>0.54</td>
</tr>
<tr>
<td>Stop and rest often</td>
<td></td>
<td>0.607</td>
<td></td>
<td></td>
<td>0.464</td>
<td>0.64</td>
</tr>
<tr>
<td>Eigenvalue</td>
<td>14.73</td>
<td>2.54</td>
<td>1.74</td>
<td>1.37</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Variance</td>
<td>0.53</td>
<td>0.09</td>
<td>0.06</td>
<td>0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proportion of total variance</td>
<td>0.53</td>
<td>0.62</td>
<td>0.68</td>
<td>0.73</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alpha</td>
<td>0.93</td>
<td>0.91</td>
<td>0.89</td>
<td>0.88</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

KMO = Kaiser–Meyer–Olkin estimate of sampling adequacy. Overall KMO 0.835.
Blank cells have factor loadings of <0.4.
Alpha (Cronbach) is a measure of scale reliability.

was 0.832 (95% CI 0.744–0.921), the uraemia scale was 0.753 (95% CI 0.632–0.874) and the anaemia scale was 0.850 (95% CI 0.770–0.928).

Discussion

Although most healthcare providers recognize the need to elicit symptoms in patients they treat, it is now becoming clear that without adequate questioning, symptom burden in patients with CKD is often poorly recognized [14]. Patients with greater severity and prevalence of symptoms have poor health-related quality of life [1], which in turn is associated with poor outcomes [15]. This study provides an instrument to measure the presence and the severity of symptoms in patients with CKD not treated with dialysis. Four domains of symptoms were recognized that could be broadly classified as neuropsychiatric, uraemic, anaemic and cardiovascular symptoms. These scales had a high degree of internal reliability, i.e. the items within the domain measured a similar concept or cluster. Divergent validity was established by comparing these symptom domains with objective and subjective markers. There was good to excellent test–retest reliability within each domain.

Systematic studies of symptoms in patients with CKD not on dialysis are not available so I can only compare the symptom prevalence seen in this study to that of ESRD [3]. Murtagh et al. reported that fatigue/tiredness was experienced by 70–80% of ESRD patients, pruritis and constipation by 50–60%, anorexia, pain and sleep problems by 40–50% and anxiety, shortness of breath and nausea by 30–40% of the patients [3]. In this study, the top five symptoms of at least moderate severity in decreasing order of prevalence were tire more easily, limited physical activity, nocturia, joint pain and stop and rest often. Pruritis bothered 52%, constipation 33%, anorexia 18%, nausea 25%, poor sleep quality 51% and shortness of breath 33% of the patients. Thus, it appears that symptom burden is quite high.
Fig. 3. Dendrogram of (dis)similarity between subdomains of KDQOL and the newly created scale (in capitals). Dendrogram was generated using complete linkage cluster analysis.

in patients with CKD, except that nausea and anorexia may be less common.

I found no relationship between uraemic symptoms such as poor appetite and nausea and the stage of kidney disease. This may have been due to few patients with advanced renal failure who have a high symptom burden [16]. For example, Murphy et al. reported that in 55 older patients with stages 4 and 5 CKD who were managed without dialysis, the prevalence of anorexia was 58% [5]. Another reason for the lack of relationship between CKD stage and symptoms could be that such a relationship may not exist and at least some evidence exists to support this notion. At least one multicentre study measuring health-related quality of life in patients with CKD not on dialysis did not find an association between the quality of life and GFR [6]. Even in advanced stage CKD, Murphy et al. did not find any relationship between the severity of CKD and symptoms [5]. Thus, it appears that the complications that emerge from CKD such as anaemia may be more important for the genesis of symptoms than simply uraemia.

Naming factors with meaningful terms to describe the domain they measure may be difficult and controversial. For example, diarrhoea may not be considered a neuropsychiatric symptom but patients with irritable bowel syndrome may experience this symptom. Similarly, cramps and joint pains may not be cardiovascular symptoms except when diuretic use may provoke fluid-electrolyte imbalance and aggravate muscle cramps and diuretic-induced hyperuricaemia may provoke gout. Whereas the domain named anaemia contains items that are commonly recognized to be due to anaemia, such as fatigue and change in colour of the skin, some of the other symptoms may be attributable to iron deficiency. For example, altered taste and restless legs may be due to iron deficiency per se rather than anaemia [11]. Therefore, it appears that the symptom complexes the factors represent are satisfactorily described by the named terms.

There are several limitations of this study. Item generation is an iterative process using qualitative data collection and review by experts. Although qualitative data was collected from a limited number of patients with a wide variety of kidney diseases spanning from nephrotic syndrome with normal GFR to stage 5 CKD, the items were not reviewed by experts. Therefore, the complete range of symptoms may not have been captured. A larger number of factors may be extracted if more subjects with much lower GFR were recruited into the study. Given the limited number of subjects, the results of this analysis should be considered preliminary. The results of this study likely apply only to men who constituted the majority of this sample. The responsiveness of this instrument to interventions that treat anaemia, improve uraemia or cardiovascular function will require further studies. Finally, a much larger number and diverse group of patients such as younger patients and those without diabetes are needed to confirm these novel observations. A larger sample size with longitudinal follow-up is needed to better assess the responsiveness of the questionnaire to progression of CKD. A larger sample size will also allow better assessment of the influence of comorbid and demographic factors on symptoms. Such studies are in progress.

In conclusion, this instrument developed for use in patients with CKD not on dialysis fills a need to objectively measure symptom burden in this population. The high
symptom burden correlates with some known disease states (heart failure) and established tests (haemoglobin) but not with others (such as GFR). Given the excellent coefficient alpha, test–retest reliability, and validity it appears that this instrument may be useful for the assessment and follow-up of symptom burden of patients with CKD. Incorporating such an instrument in routine practice and clinical trials may allow measurement of outcomes that may be more relevant to patients.

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References


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Outcomes predicted by phosphorous in chronic kidney disease: a retrospective CKD-inception cohort study

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Abstract

Background. The impact of secondary hyperparathyroidism on morbidity and mortality among patients with chronic kidney disease (CKD) is unclear.
Methods. We conducted a retrospective cohort study to investigate the relationship between CKD and serum phosphorous. Through clinical databases at a large health maintenance organization, we identified a dynamic CKD inception cohort between 1997 and 2004, with stage 3–5 kidney disease with subsequent phosphorous measurement; the patients were followed up for up to 5 years for outcomes of mortality, cardiovascular mortality, cardiovascular...