Towards a Symptom Cluster Model in Chronic Kidney Disease: A Structural Equation Approach

ABSTRACT

Aims: To test a symptom cluster model in chronic kidney disease patients based on the Theory of Unpleasant Symptoms, accounting for the relationships between influencing factors, symptom experience, and consequences for quality of life.

Background: The evaluation of symptom clusters is a new field of scientific inquiry directed toward more focused symptom management. Yet, little is known about relationships between symptom clusters, predictors, and the synergistic effect of multiple symptoms on outcomes.

Design: Cross-sectional.

Methods: Data were collected from 436 patients with advanced stages of chronic kidney disease during July 2013- February 2014 using validated measures of symptom burden and quality of life. Analysis involved structural equation modeling.

Results: The final model demonstrated good fit with the data and provided strong evidence for the predicted relationships. Psychological distress, stage of chronic kidney disease, and age explained most of the variance in symptom experience. Symptom clusters had a strong negative effect on quality of life, with fatigue, sexual symptoms and restless legs being the strongest predictors. Overall the model explained more than half of the deterioration in quality of life. However, a reciprocal path between quality of life and symptom experience was not found.

Conclusions: Interventions targeting symptom clusters could greatly improve quality of life in patients with chronic kidney disease. The symptom cluster model presented has important

clinical and heuristic implications, serving as a framework to encourage and guide new lines of intervention research to reduce symptom burden in chronic kidney disease.

CONTRIBUTION OF THE PAPER

Why is this research needed?

- Identification of symptom clusters is beginning to emerge in chronic kidney disease.

- Associations between symptom clusters, patient characteristics, and quality of life are not fully understood.

- The Theory of Unpleasant Symptoms has been used extensively to guide symptom research in cancer but not in other chronic diseases.

What are the key findings?

- This study is the first to develop a symptom cluster model for patients with advanced stages of chronic kidney disease that was guided by the Theory of Unpleasant Symptoms.

- Many of the predicted relationships were supported empirically, encouraging clinical attention to assessment and intervention targeting symptom clusters to improve quality of life in chronic kidney disease patients. The model also points to key psychological and physiological contributors to the symptom experience.

How should the findings be used to influence policy/practice/research/ education?

- Interventions targeting symptom clusters could greatly improve quality of life in chronic kidney disease patients.

- The chronic kidney disease symptom cluster model supports the development of innovative management strategies in renal nursing practice and can stimulate future research to test and refine the model in clinical settings.

INTRODUCTION

Chronic kidney disease (CKD) is rapidly increasing globally due to the increasing incidence of diabetes and hypertension as well as the ageing population (Jha *et al.* 2013). It is an emerging contributor to the global burden of chronic disease (Couser *et al.* 2011; Eckardt *et al.* 2013). The disease is often unrecognised until much later when some early symptoms begin to appear, and this is largely due to the slow and insidious decline in renal function over months or years (Bonner & Douglas 2014). The final stage or end stage kidney disease is when end-organ failure has been reached, and kidney replacement therapy or conservative management begins.

Symptoms are subjective experiences that indicate changes in normal functioning and affect everyday life (Lenz *et al.* 1997). Conceptually, the symptom experience captures the multidimensional features of symptoms to account for the different levels of severity, distress and frequency (Jablonski 2007; Lenz & Pugh 2014), although in chronic kidney disease (CKD) where symptom burden is high there has been a paucity of research (Danquah *et al.* 2010; Jablonski 2007). Symptoms are likely to be related to each other, may share the same aetiology, and can occur together, forming a symptom cluster (Kim *et al.* 2005). In cancer, the evaluation of symptom clusters is a more advanced field of scientific inquiry (Dodd *et al.* 2001; Miaskowski 2006), which has contributed to the simplification of symptom management to that targets multiple symptoms at the same time (Williams 2007). Emerging evidence in oncology suggests that interventions targeted at the symptom cluster level, such as a psychoeducational approach to manage anxiety, breathlessness and fatigue, are effective (Berger *et al.* 2013; Chan *et al.* 2011; Kwekkeboom *et al.* 2012; Xiao *et al.* 2016). However, in CKD, effective symptom management is a challenge for clinicians, and it is likely due the lack of understanding about the relationships between the antecedent patient characteristics, the symptom experience, and the synergic effect of multiple symptoms on outcomes.

Development of a model that explains these relationships is, therefore, a necessary step to improving the well-being of people with CKD.

Background

There is international evidence that living with CKD is associated with considerable symptom burden, with people reporting up to 20 symptoms which affect everyday life (Murtagh *et al.* 2007; Weisbord *et al.* 2005; Yong *et al.* 2009). Fatigue, pain and sleep disturbance are highly prevalent, severe and distressing symptoms (Almutary *et al.* 2016a; Murtagh *et al.* 2007; Weisbord 2005, 2007). A growing body of evidence suggests that symptoms in CKD occur in clusters (Almutary *et al.* 2016b; Amro *et al.* 2014; Jablonski 2007; Lee & Jeon 2015; Thong *et al.* 2009; Yu *et al.* 2012), underscoring that symptom management strategies that target single symptoms in patients with CKD are suboptimal (Davison & Ferro 2009; Weisbord 2007; Williams & Manias 2008). However, less is known about the relationships between the symptom clusters and patient characteristics, as well as the impact of symptom clusters on patient outcomes (e.g. quality of life).

While symptom cluster research is emerging in CKD, most of the studies identified symptom clusters from a limited number of primarily physical symptoms (11 to 17) and using only one symptom dimension (Amro *et al.* 2014; Jablonski 2007; Lee & Jeon 2015; Thong *et al.* 2009; Yu *et al.* 2012). However, in our recent study (Almutary *et al.* 2016b), 32 symptoms were assessed in patients with advanced CKD (stage 4 and 5) according to occurrence, severity, distress and frequency. Five distinct symptom clusters (i.e. fluid volume, sexual, neuromuscular, gastrointestinal, and psychological) were identified that were stable across all symptom dimensions. Associations between age (Lee & Jeon 2015), gender (Lee & Jeon 2015; Yu *et al.* 2012), and level of depression and symptom clusters have been reported in patients with CKD (Amro *et al.* 2014; Yu *et al.* 2012). In addition, symptom clusters were found to have a negative impact on quality of life (Amro *et al.* 2014; Lee & Jeon 2015;

Thong *et al.* 2009), and functional status (Thong *et al.* 2009) as well as increased mortality rates in dialysis patients (Amro *et al.* 2015). However, the causal relationships among symptom clusters, predictors (influencing factors), and consequences have not been fully examined in CKD. Knowledge of these relationships would increase our understanding of the symptom experience of patients with CKD. An examination of these inter-relationships should be guided by a theoretical framework.

Theoretical framework

Several theories have been used to guide symptom management research and studies examining symptom clusters (Brant *et al.* 2010). Of these, the Theory of Unpleasant Symptoms (TOUS) was revised to include multiple concurrent symptoms (Lenz & Pugh 2014; Lenz *et al.* 1997). The TOUS assumes that symptoms can occur alone or with multiple other symptoms, and could concurrently occur resulting in multiple relationships and interactions between and among symptom (Lenz & Pugh 2014; Lenz *et al.* 1997). The TOUS consists of three major reciprocal concepts: influencing factors, symptom experience, and consequences. Physiological, psychological and situational factors influence the symptom experience. The symptom experience accounts for the multidimensional aspects of a single symptom or symptom clusters (Lenz & Pugh 2014). According to the TOUS, the consequence is the outcome or impact of the symptom experience on an individual's functional and/or cognitive performance. The theory includes feedback loops to indicate that influencing factors can affect the symptom experience, symptoms can affect consequences, and consequences can in turn affect influencing factors and the symptom experience (Lenz & Pugh 2014; Lenz *et al.* 1997).

The advantages of the TOUS include the acknowledgement of concurrent relationships among multiple symptoms consistent with symptom clusters, the simplicity of its constructs, its ability to capture the multidimensional nature of symptoms, and the ease with which it can

be used to conceptualize the symptom experience and test the relationships between and among the symptoms (Brant *et al.* 2010). The theory also assumes reciprocal interactions between the three concepts, that may help in understanding the complex nature of the overall symptom experience (Lenz & Pugh 2014).

Only a few studies in cancer have applied the TOUS to examine direct relationships between constructs (Oh *et al.* 2012; So *et al.* 2013) or reciprocal relationships proposed by the theory (Hoffman *et al.* 2009). The purpose of this study was to use the TOUS as a guide to develop and test a CKD symptom cluster model (Figure 1), to examine relationships between influencing factors (patient characteristics), symptom experience, and consequences on quality of life. Structural equation modeling (SEM) was used to test the overall model fit because it is based on a confirmatory approach, allows an examination of the relationships among the measured (observed) and latent variables in the hypothesized model, and accounts for measurement error (Byrne 2013). We included the major concepts of the TOUS and build on our previous work on symptom clusters in advanced CKD (Almutary *et al.* 2016b).

THE STUDY

Aim

To test a symptom cluster model in chronic kidney disease patients based on the Theory of Unpleasant Symptoms, accounting for the relationships between influencing factors (patient characteristics), symptom experience, and consequences for quality of life.

Design

Structural equation modeling (SEM) with cross-sectional data was used to test the hypothesized model.

Participants

The details of this cross-sectional study are published elsewhere (Almutary *et al.* 2016b). Briefly, a convenience sample of 436 people with advanced stages of CKD was recruited from kidney centers and nephrology clinics in three large tertiary hospitals between July 2013 and February 2014. Eligible patients were over 18 years of age, diagnosed with either stage 4 or 5 CKD with estimated Glomerular Filtration Rate (eGFR) < 30 mL/min/1.73m^2, or currently receiving dialysis (either haemodialysis or peritoneal dialysis). Patients with cognitive impairment and those with critical conditions were excluded.

The recommended sample size for SEM is 10-20 cases for each estimated parameter (Byrne 2013; Kline 2015). In this study with 30 parameters, a minimum of 300 people with CKD was needed to have adequate power for the SEM.

Data collection

After obtaining written, informed consent, patients completed self-report questionnaires face-to-face with one researcher to ensure consistent instructions for all patients (especially for those with low literacy levels), and reduce the amount of missing data. Clinical variables were collected from both dialysis charts and hospital files.

Measures

Guided by the TOUS, we operationalized the key variables for the hypothesized model using validated measures. Also we assessed the validity of the measurement model for each latent construct.

Symptom experience

The CKD Symptom Burden Index (CKD-SBI) assesses the occurrence, distress, severity, and frequency of 32 CKD symptoms during the previous 4 weeks (Almutary *et al.* 2015). Occurrence was coded as the presence or absence of each symptom (yes/no) and can range from 0-32 symptoms. Other symptom dimensions (distress, severity and frequency) were rated on a 0 to10 numerical rating scale. Participants rate the "distress" dimension from

none to *very much*, "severity" from *none* to *very severe*, and "frequency" from *never* to *constant*.

Using exploratory factor analysis (EFA), five symptom clusters across all four symptom dimensions and the core symptoms within each cluster were identified (Almutary *et al.* 2016b). These symptom clusters were fluid volume (cough, shortness of breath, chest pain, light headedness or dizziness, and difficulty concentrating), sexual (decreased interest in sex and difficulty becoming sexually aroused), gastrointestinal (nausea and vomiting), neuromuscular (muscle soreness and numbness or tingling in feet), and psychological (feeling sad, feeling anxious, worrying, depression and feeling nervous). These clusters were stable across all symptom dimensions (i.e. occurrence, distress, severity and frequency). In addition, three interconnecting (or mega) symptoms (fatigue, restless legs, and sleep disturbance) that were strongly associated with several of the symptom clusters were identified (see Almutary *et al.* 2016b for further explanation). The factor scores for the core symptoms within each symptom cluster and the three interconnecting symptoms were used as indicators of the latent construct of symptom experience conceptualized by the TOUS (Lenz & Pugh 2014). The factor scores in EFA were obtained using the regression scores method (Polit 2010).

The measurement model for the latent construct of symptom experience was assessed using confirmatory factor analysis. The results indicated that the measurement model of symptom experience fits the data adequately (GFI = 0.97; AGFI = 0.94; CFI = 0.96; TLI = 0.96; RMSEA = 0.06 with 90% CI = 0.04-0.09). Internal consistency was satisfactory for symptom clusters, Cronbach's alphas ranged between 0.74 and 0.90. The composite reliability of the symptom experience was 0.88.

Influencing factors (patient characteristics)

Physiological and situational characteristics. The physiological characteristics that were consistently reported in the literature as correlated with individual symptom experience

were age (Almutary *et al.* 2013; Caplin *et al.* 2011; Lee & Jeon 2015) and stage of CKD (Almutary *et al.* 2016a; Dong *et al.* 2014). Disease stage was categorized as stage 4, 5, and late stage 5 to assess the impact of reduced kidney function on symptom experience and to indicate treatment modality. The relationships between the comorbidities and symptom burden are not well examined in the literature. However, there is likely to be a relationship between comorbid health conditions (e.g. cardiovascular disease) and CKD symptom burden (Thong *et al.* 2009), although this may be confounded by dialysis treatment modality (Yong *et al.* 2009). We hypothesized that the presence of comorbidities is another important influencing factor that could affect the symptom experience. In this study, the number of comorbidities was estimated using Davies et al.'s (2002) co-morbidity index, which consists of seven domains. Total scores can range from 0 to 7. The scores are categorized into three groups: grade 0 (no comorbidities), grade 1 (1-2 comorbidities), or grade 2 (3-7 comorbidities).

Some evidence suggests that a weak correlation exists between symptoms in patients with CKD and clinical biomarkers (e.g. albumin, calcium, potassium) (Almutary *et al.* 2016a; Amro *et al.* 2014; Thong *et al.* 2009). In this study, no significant bivariate associations were found between clinical biomarkers (i.e. albumin, phosphate, calcium, potassium, haemoglobin) and CKD symptom clusters. Therefore, no clinical variables were included in the hypothesized model.

Of the situational factors in the CKD symptom model, female gender is a predictor of increased symptom burden in CKD (Almutary *et al.* 2016a; Lee & Jeon 2015; Yu *et al.* 2012) although Amro et al. (2014) were unable to demonstrate this correlation. Due to the inconsistent findings, gender was included in the model as a potential influencing factor.

Psychological factors. In the TOUS, psychological factors reflect both emotional and cognitive characteristics, such as mood state during the time of the symptom experience,

emotional responses to the illness, or a symptom itself (Lenz & Pugh 2014). It is unclear whether influencing psychological factors are state or trait characteristics, or both (Brant *et al.* 2010). The ways of treating psychological factors in the literature have caused some conceptual confusion (Lenz & Pugh 2014). For example, across several studies, depression is considered to be an influencing factor, a symptom itself, or even a consequence (Abdel-Kader *et al.* 2009; Brant *et al.* 2010; Son *et al.* 2009). Noquez (2008) noted that the TOUS focused strictly on physical symptoms and considered psychological symptoms, such as anxiety and depression, as influencing factors rather than symptoms.

In this study, we used psychological distress captured by the psychological symptom cluster as an influencing factor on CKD symptom experience for several reasons. First, consistent with our hypothesized model, many studies have demonstrated that psychological problems, such as depression have a negative influence on the CKD symptom experience (Abdel-Kader *et al.* 2009; Son *et al.* 2009; Weisbord *et al.* 2005; Yamamoto *et al.* 2009; Yu-Sen *et al.* 2007). Recently, for example, Amro et al. (2014) found that two symptom clusters in dialysis patients (i.e. uraemic and neuromuscular) were independently associated with depression (measured using the Beck Depression Inventory). Second, treating the psychological symptom cluster as an influencing factor minimized conceptual overlap between the theory's concepts. As the TOUS (Lenz & Pugh 2014) indicates, emotional symptoms can be an influencing psychological factor that can increase the symptom experience.

Consequence

Consequence is the outcome or impact of the symptom experience on an individual's functional and/or cognitive performance (Lenz & Pugh 2014; Lenz *et al.* 1997). The consequence of symptom experience in this study is quality of life (QOL), a significant clinical outcome in CKD (Breckenridge *et al.* 2015; Wyld *et al.* 2012). Previous research has

found that symptom clusters independently predict QOL in CKD (Amro *et al.* 2014; Lee & Jeon 2015; Thong *et al.* 2009).

The Kidney Disease Quality of Life short form (KDQOL-36™) is a widely used instrument and available in Arabic (Abd Elhafeez *et al.* 2012; Al Jumaih *et al.* 2011). It includes 36 self-report items that measure 5 subscales: SF-12 to measure physical and mental components of health; burden of kidney disease; symptom problem list; and effect of kidney disease. In this study, the latent construct of QOL was developed by using scores from the physical component summary (PCS) and the mental component summary (MCS) of the KDQOL-36™ (Hays *et al.* 1994; RAND corporation n.d.). These components were selected to represent the consequence instead of a total score of QOL to avoid any possible overlap between the symptom experience (measured by the CKD-SBI) and symptoms (measured in the KDQOL-36™). The PCS score consists of total scores of physical functioning, role limitations related to physical problems, body pain, and perception of general health. The MCS score consists of total scores of mental health, role limitations related to emotional problems, vitality and social functioning. The total score of each component ranges from 0-100, with higher scores indicating a better physical and mental QOL.

The measurement model for the latent construct of QOL revealed good fit using confirmatory factor analysis (GFI = 0.97; AGFI = 0.94; CFI = 0.98; TLI = 0.97; RMSEA = 0.06 with 90% CI = 0.04-0.08). The Cronbach's alpha for the PCS was 0.84 and for the MCS was 0.74. The composite reliability QOL was 0.80.

Ethical considerations

Ethical approvals for this study were obtained from the Queensland University of Technology Human Research Ethics Committees, King Abdulaziz University Hospital, and Jeddah Research Centre Ethics Committees.

Data Analysis

Analysis was performed using IBM SPSS Statistics version 21 (IBM Corp., Armonk, NY) and AMOS version 22. Descriptive statistics were used to summarize sample characteristics and key study variables. There were few missing data in the overall measures (<5%). The pattern of missing data was assessed using Little's MCAR test and found to be missing completely at random. Accordingly, the Expectation Maximization imputation was used to substitute missing data, as this method produces unbiased estimates when there is little missing data (Musil *et al.* 2002). Data were assessed for normality and multivariate outliers. Correlations between the key variables of the study were assessed using Pearson's correlation coefficients.

Structural equation modeling (SEM), with maximum likelihood estimation, was used to test the hypothesized model. The criteria used to appraise the structural model were model fit indices, as well as the magnitude and direction of path estimates (Hair *et al.* 2014). The fit indices that were used to evaluate the proposed model were normed Chi-square (χ2/df), Goodness-of-Fit Index (GFI), Adjusted Goodness-of-Fit Index (AGFI), Comparative Fit Index (CFI), Tucker Lewis Index (TLI), Root Mean Square Error of Approximation (RMSEA) and Standardized Root Mean Square Residual (SRMR) (Byrne 2013; Hair *et al.* 2014; Kline 2011). Following the recommendation by Byrne (2013) and Kline (2011), the model was considered to have an adequate fit when the χ2/df ratio was <5, the value of both absolute fit indices (GFI and AGFI) and the comparative fit indices (CFI and TLI) were >0.90, and both RMSEA and SRMR values were <0.08.

The standardized path coefficients were assessed to examine the statistical significance and directions of path estimates that exist between the variables in the model. In addition, the squared multiple correlations (similar to R^2 in regression analysis) were evaluated to indicate the percentage of variance in the endogenous variables (dependent variables) explained by

the exogenous variables (independent variables) in the model. As the model includes reciprocal paths among the symptom experience, QOL and influencing factors, the stability index (should be < 1) was evaluated. Moreover, to determine the relative importance of symptom clusters in predicting the latent variable QOL, we examined the equivalence of path estimates similar to a multiple regression analysis. For all analyses, p <0.05 was considered statistically significant.

Validity and reliability

The validity and reliability of instruments used in this study have been previously reported. The CKD-SBI was translated and validated in Arabic (Almutary *et al.* 2015). The CKD-SBI has good internal consistency (Cronbach's alpha = 0.91), and discriminative and convergent validity (Almutary *et al.* 2015). The KDQOL-36™ is a widely used instrument and has been previously validated in Arabic; demonstrating good psychometric properties (Abd Elhafeez *et al.* 2012; Al Jumaih *et al.* 2011). In this study, Cronbach alpha scores were 0.84 for the PCS and 0.74 for the MCS. In addition, the validity of the measurement model for each latent construct was assessed using confirmatory factor analysis.

RESULTS

Sample characteristics

A total of 436 participants completed the study measures. Mean age was 48.3 years (SD 14.9), ranging between 18-87 years, and 53% were male. Most (75.5%) had commenced dialysis therapy. More than half of the patients (58.3%) had at least one co-morbid condition. The mean PCS score was 44.76 (SD = 30.49) and the mean MCS was 56.88 (SD = 25.37). Table 1 provides a summary of the sample characteristics of this study.

The correlation matrix of the key variables included in the final analysis is presented in Table 2. Negative correlations of at least 0.30 were found between all symptom clusters and QOL domains.

Overall model fit

The initial result for the overall model indicated an inadequate model fit: (χ^2/df = 5.2; GFI = 0.89; AGFI = 0.85; CFI = 0.80; TLI = 0.76; RMSEA = 0.11 with 90% CI = 0.09-0.11). The stability index of the model found to be 0.29, indicating a stable interaction between the key variables of the model. Respecification of the hypothesized model was considered to improve the model fit. This re-specification was guided by TOUS during assessment of the standardized path coefficients and modification indices (Hair *et al.* 2014; Kline 2015). Accordingly, one influencing factor (gender) was eliminated from the model, as the estimated path was non-significant. Also, the errors for restless legs and both neuromuscular and fluid volume clusters were set to be correlated. This decision was made based on the significant relationships suggested by the modification indices and the clinical significance of these correlations (as all symptoms/clusters are due to advanced stages of CKD and the worsening uraemic syndrome) (Chikotas *et al.* 2006). The reciprocal relationship between the latent constructs (i.e. symptom experience and QOL) was assessed. These relationships produced unstable estimates (unacceptable parameter estimates). Therefore, this proposed reciprocal relationship was eliminated from the final model.

Figure 2 presents the final model with standardized path estimates. Overall, fit statistics for the final model demonstrated a good fit based on goodness-of-fit statistics: (χ^2/df = 3.3; GFI = 0.94; AGFI = 0.91; CFI = 0.92; TLI = 0.91; RMSEA = 0.07 with 90% CI = 0.06-0.07; SRMR = 0.06).

Direct effects between influencing factors, symptom experience and consequence

The strongest predictor of symptom experience was psychological distress (β = 0.57, p < 0.001), followed by stages of CKD (β = 0.49, p < 0.001) and age (β = 0.34, p < 0.001). Together the influencing factors explained 68% of the variance in symptom experience scores.

The fluid volume symptom cluster (β = 0.62), fatigue (β = 0.62) and sleep disturbance (β = 0.59) loaded strongly on the latent variable symptom experience. The results demonstrated that symptom experience had a strong negative direct effect on QOL (β = -0.75, p <0.001). Together the influencing factors and symptom experience explained 57% of the variance in QOL.

To examine which symptom clusters were the strongest predictors of QOL, we modelled these relationships in Figure 3.The standardized estimates (β) for each symptom variable show that fatigue (β = -0.31, p <0.001), followed by the sexual symptom cluster (β = -0.25, p <0.001) and restless legs (β = -0.15, p = 0.003) were significant predictors.

DISCUSSION

The aim of this study was to develop a CKD symptom cluster model based on the TOUS and test these relationships in a large cohort of people with advanced stages of CKD. The study builds on our previous work that identified symptom clusters in CKD to represent the latent construct of symptom experience in the hypothesized model (Almutary *et al.* 2016b). Thus a major contribution of this study is an explanatory model of the relationship between the high symptom burden and poor QOL experienced by this population which provides theory-based evidence to inform nursing practice. Many of the predicted relationships were supported empirically, encouraging clinical attention to assessment and intervention targeting symptom clusters to improve QOL. As guided by the TOUS, the model

will also enable nurses to design interventions in a way that takes into account the multidimensional and interactive nature of symptoms, influencing factors and consequences, thereby making them person-centred.

Translation of symptom cluster research into renal nursing practice would be supported by the adoption of comprehensive assessment tools such as the CKD-SBI and a multidisciplinary team-based approach to symptom management. Symptom measures that are commonly used in practice and research, such as the Palliative Care Outcome Scale – Symptoms Renal (POS-S Renal) and KDQOL-36™ symptom problem list, are too narrow to capture the CKD symptom experience (Almutary *et al.* 2016b). Even if renal nurses do identify troubling symptom clusters, they may not be adequately supported in current systems to initiate comprehensive management. Innovative models of care, such as integrating a renal supportive (palliative) care program as part of healthcare services for those in advanced stages of CKD, are needed to improve symptom management (Davison *et al.* 2015). Some symptoms deserve routine focused assessment. Given the interconnection between fatigue and all symptom clusters (Almutary *et al.* 2016b) and its significant impact on QOL, the multidimensional assessment of fatigue as a sentinel symptom in CKD could be used to trigger more comprehensive assessment of symptom burden, which improves nursing knowledge for clinical practice.

The CKD symptom cluster model also points to key psychological and physiological contributors to the symptom experience. Future research examining underlying pathophysiological mechanisms of CKD symptom clusters will be an important contribution to the field. However, consistent with previous research using the TOUS, psychological distress was the strongest predictor of symptom experience (Lenz & Pugh 2014). We tested an alternative model in which psychological distress was an indicator of symptom experience, but it demonstrated poor fit. Psychological factors can influence the perception of

physical symptoms directly (e.g. sleep disturbance) (Pai *et al.* 2007) or indirectly through the effect on treatment adherence. The impact of psychological factors such as depression and anxiety on treatment adherence in CKD have been reported previously (Kimmel 2002; Tijerina 2006). For example, depression could reduce adherence to fluid and dietary restrictions, which then contributes to the worsening of the fluid symptom cluster. While other studies have found an association between psychological factors and CKD physical symptoms (Abdel-Kader *et al.* 2009; Son *et al.* 2009; Weisbord *et al.* 2005; Yamamoto *et al.* 2009; Yu-Sen *et al.* 2007), this study is the first to demonstrate the strength and direction of this relationship in the context of the overall CKD symptom experience.

Our findings show that fatigue, sexual symptoms and restless legs have the greatest impact on QOL. Previous studies have consistently reported a high level of fatigue in patients with various CKD stages and dialysis modalities (Artom *et al.* 2014; Bonner *et al.* 2008, 2010). Fatigue is a pervasive contributor to the CKD symptom experience and is known to interconnect with a range of symptom clusters (Almutary *et al.* 2016b). Effective management of symptom clusters is likely to alleviate the burden of fatigue, thereby improving the overall symptom experience in CKD. In addition, fatigue significantly affects the ability to perform ordinary activities (e.g. self-care and social activities) in CKD patients (Bonner *et al.* 2010). As a result, rehabilitative interventions such as energy conservation and individualized exercise regimens need to be incorporated into nursing care plans to reduce the impact of fatigue on daily activities and support independent living.

Several studies demonstrated the negative impact of impaired sexual function among those with CKD and their QOL (Basok *et al.* 2009; Fernandes *et al.* 2010; Sumii *et al.* 2016). Sexual dysfunction can negatively affect social and marital relationships, self-esteem and sense of wholeness (Basok *et al.* 2009). The young age of our participants may have also contributed to greater concerns about interpersonal relationships, which would greatly

influence their QOL. However, there is still under-recognition of the issues associated with sexual symptoms in clinical practice, which require more attention to address the hidden factors affecting QOL (Fernandes *et al.* 2010).

Interestingly, we could not demonstrate a feedback loop from QOL to symptom experience as proposed by the TOUS. Conceptually, it seems plausible that performance outcomes such as QOL influence the experience of unpleasant symptoms (Lenz & Pugh 2014). Using cross-sectional data to model non-recursive relationships is a known limitation and a longitudinal time-lagged design may produce more stable estimates (Wong & Law 1999). However, exploring these relationships is challenging in CKD because of the slow progressive nature of the disease and its symptoms, and the likely response shift that occurs in QOL over a long period of time (Amro *et al.* 2016). Many people remain asymptomatic and undiagnosed until 90% of kidney function is lost (James *et al.* 2010). Nevertheless, longitudinal studies are needed to validate the reciprocal relationships proposed by the TOUS. For instance, symptoms and quality of life alterations along the CKD trajectory (i.e. from initial diagnosis to the development of end stage kidney disease, or studying the effect of KRT. Both of these studies would need to follow patients for several years.

Limitations

There are several limitations of this study that warrant consideration. Some potentially important influencing factors were not captured in our model, such as social support and spiritual beliefs (Lenz & Pugh 2014), which warrant future research. Also, our data were collected from patients from one cultural background. While previous research suggests no significant differences in symptom experience across cultures (Moser *et al.* 2014), further studies to validate these findings are required that specifically focus on older patients with multiple comorbid conditions. The mean age of the participants in this study was younger

than other countries although this is consistent with annual report of dialysis patients in the Saudi Center for Organ Transplantation (2015). The younger age in Saudi Arabia is mostly due to the increasing incidence of diabetes and hypertension, the poor screening and detection of CKD, and the late referral to nephrology services (Al-Sayyari & Shaheen 2011; Farag *et al.* 2012). Being younger may also explain the low comorbidity scores in our sample. Nevertheless the model fitted with this population, and it is likely that an older sample with more comorbidities would have strengthened the relationship of influencing factors on the symptom experience and QOL (a situation experienced by clinicians in dialysis units). The advantage to practice is that the TOUS fits with and explains the poor QOL of patients with advanced stages of CKD. We do, however, recommend repeating this study in an older group of patients with extensive comorbid conditions. Finally, using self-report measures for both symptoms and outcomes may introduce common method variance. However, using validated measures to construct latent variables should minimize this issue (Meade *et al.* 2007; Spector 2006).

CONCLUSION

Symptom burden is under-recognized and not well managed in routine renal practice although it is the most important predictor of reduced QOL among people with CKD. The present study adds to a growing body of evidence that conceptualizing individual symptoms as clusters within a biopsychosocial framework such as the TOUS, offers a clinically meaningful and evidence-based approach to symptom management. We have demonstrated that using symptom clusters to represent the total symptom experience is able to explain the relationships between patient characteristics and outcomes. The model can be used to inform the development and testing of cluster-targeted symptom interventions for patients with advanced CKD.