Assessment of treatment burden and its impact on quality of life in dialysis-dependent and pre-dialysis chronic kidney disease patients

Asmaa Al-mansouri [a], Fadwa Saqr Al-Ali [b], Abdullah Ibrahim Hamad [b], Mohamed Izham Mohamed Ibrahim [c], Nadir Kheir [d], Rania Abdelaziz Ibrahim [b], Muna AlBakri [a], Ahmed Awaisu [c,*]

[a] Department of Pharmacy, Hamad Medical Corporation, Doha, Qatar
[b] Nephrology Division, Hamad Medical Corporation, Doha, Qatar
[c] Department of Clinical Pharmacy and Practice, College of Pharmacy, QU Health, Qatar University, Doha, Qatar
[d] College of Pharmacy and Health Sciences, Ajman University, Ajman, United Arab Emirates

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ABSTRACT

Background: The management of chronic kidney disease (CKD) and its complications places a significant burden on patients, resulting in impairment of their health-related quality of life (HR-QOL). Little is known about treatment-related burden in pre-dialysis and hemodialysis (HD) CKD patients.

Objective: This study aimed to investigate the magnitude of treatment-related burden and its impact on HR-QOL among patients with CKD.

Methods: This was a prospective, cross-sectional study to assess treatment-related burden and HR-QOL among patients with CKD in Qatar. Treatment-related burden and HR-QOL were assessed quantitatively using the Treatment Burden Questionnaire (TBQ) and the Kidney Disease Quality of Life (KDQOL™) questionnaire, respectively. The total TBQ score ranges from 0 to 150, with a higher score indicating higher treatment burden, while the range of total possible scores for the KDQOL™ are from 0 to 3600 with higher transformed score indicating better QOL. Pre-dialysis and hemodialysis (HD) CKD patients who had regular follow-up appointments at Fahad Bin Jassim Kidney Center in Qatar were enrolled. Data were analyzed descriptively and inferentially using SPSS version-24.

Results: Two hundred-eighty CKD patients (HD = 223 and pre-dialysis = 57) were included in the analyses (response rate 60.9%). Approximately 35% of the participants reported moderate to high treatment-related burden (TBQ global score 51–150). HD patients experienced significantly higher treatment burden compared to pre-dialysis patients with a median (IQR) score of 45 (36) versus 25 (33), respectively (p < 0.001). Medication burden and lifestyle changes burden were the highest perceived treatment-related burden. Overall, the perceived median (IQR) HR-QOL measured using the KDQOL-36™ among the participants was 2280.6 (1096.2) compared to the maximum global score of 3600. Similarly, the HD patients demonstrated significantly lower HR-QOL compared to the pre-dialysis patients [median (IQR) score of 2140 (1100) vs. 2930 (995), respectively; p < 0.001]. There was a strong negative correlation between TBQ score and KDQOL-36™ score [rs (251) = −0.616, p < 0.001], signifying that HR-QOL decreases as treatment burden increases.

Conclusions: This study suggests that a considerable proportion of CKD patients suffered from treatment-related burden and deterioration in HR-QOL at a varying degree of seriousness. HD patients experienced significantly higher burden of treatment and lower HR-QOL compared to pre-dialysis patients and that HR-QOL declines as treatment burden increases. Therefore, treatment-related burden should be considered in CKD management and factors that increase it should be considered when designing healthcare interventions directed to CKD patients.

* Corresponding author. Department of Clinical Pharmacy and Practice, College of Pharmacy, Qatar University, Doha, Qatar.
E-mail address: aawaisu@qu.edu.qa (A. Awaisu).

Introduction

Chronic kidney disease (CKD) encompasses a spectrum of five stages of kidney damage, ranging from very mild damage in stage 1 to complete kidney failure in stage 5. CKD is associated with a significant health and economic burden worldwide. In 2016, the global prevalence of CKD was 13.4%.[1] End stage renal disease (ESRD), defined as having an estimated glomerular filtration rate (eGFR) of <15 mL/min, is approaching an epidemic proportion due to an increasing aging population, diabetes prevalence and other co-morbidities. From 2009 to 2015, ESRD annual incidences significantly increased by 7.5%.[2] CKD is associated with an increased morbidity, cardiovascular-related mortality, and hospitalization.[3] CKD in general and ESRD in particular contribute to a high economic burden on the health care system worldwide. According to the United States Renal Data System, 7.1% of the Medicare cost was attributed only to ESRD patients; $33.9 billion was contributed to Medicare-associated costs in 2015.[4] Data available on the incidence, prevalence and epidemiological factors at different stages of CKD in Arab countries are very limited. Based on limited data registries and some small studies, an almost similar disease pattern has been reported in Middle Eastern countries. In 2010, the calculated incidence of ESRD in Middle Eastern countries was 140 cases per million population (pmp).[5] Specifically, the estimated incidence and prevalence of ESRD in Qatar were 122 cases pmp and 480 cases pmp, respectively.[6]

The process of progression from one stage of CKD to another is associated with worsening symptoms and complications. The prevalence of cardiovascular morbidity and mortality is extremely elevated across different CKD stages.[7–10] The most commonly reported CKD co-morbidities and complications in the literature are hyperparathyroidism, anemia, hypertension, fluid and electrolyte imbalance, bone mineral disorder, metabolic acidosis, diabetes, dyslipidemia, and others.[11–13] Patients with ESRD are expected to have an average of six different chronic medical conditions.[14] In addition to disease co-morbidities and complications, CKD patients experience daily burdensome symptoms (fatigue, pruritus, constipation, anorexia, pain, sleep disturbances, anxiety, dyspnea, nausea, restless leg syndrome and depression).[15] These symptoms will gradually lead to worsening of patients' health-related quality of life (HR-QOL).[16,17] In addition to symptoms burden, there are other factors that contributes to the overall perceived HR-QOL and these include medication and overall treatment burden. Medication-related burden plays a central role in shaping patients HR-QOL, since dialysis patients are prescribed a median of 19 pills per day.[18] In particular, patients undergoing hemodialysis (HD) are prescribed an average of 8–12 medications at a time.[14,19–23] Moreover, deterioration of physical components of HR-QOL measured using short-form 36 (SF-36) QOL questionnaire was associated with a higher pill burden in dialysis patients with 62% of the patients not adherent to phosphate binders.[18]

Treatment burden is a new emerging concept in the field of healthcare and chronic disease management. It is defined as "the workload imposed by healthcare on patients, and the effect this has on quality of life".[24] The concept has only recently gained attention by healthcare professionals and researchers worldwide.[25,26] The published literature has demonstrated that treatment burden is associated with adverse clinical and patient-reported outcomes including poor patient satisfaction with care and lower QOL, non-adherence to drug therapy, and a higher risk of all cause-hospitalization and all-cause mortality in patients with diabetes and cancer.[27,28] Treatment burden was investigated in some selected medical conditions including heart disease, diabetes, pulmonary disease and cancer.[29] To date, only little is known about treatment-related burden and its consequences on HRQOL in CKD in general and in ESRD in particular.[18,30–34] Furthermore, no previous study has attempted to quantitatively measure and compare treatment-related burden in advanced CKD patients (pre-dialysis and HD). In contrast, most previous studies among CKD patients had assessed treatment-related burden using qualitative approach.[24,25,35–37]

Given the numerous co-morbidities and complications associated with CKD as well as the high pill burden associated with the treatment of these abnormalities, it is anticipated that CKD will result in significant treatment-related burden. Therefore, there is a need to further understand the treatment-related burden in CKD and ESRD patients requiring HD using validated instruments. Using a newly developed treatment burden instrument demonstrating excellent validity and reliability[38] will enable researchers to narrow the current gap by addressing treatment burden more effectively. To the best of our knowledge, nothing is known about the magnitude and impact of treatment burden among CKD and ESRD patients requiring HD in Qatar and the Middle East region. Moreover, the relationship between treatment burden and HR-QOL in ESRD patients undergoing maintenance HD in comparison to the pre-dialysis stage has not been previously investigated. The aims of this study were to: (1) determine the magnitude of perceived treatment-related burden and HR-QOL and their association among patients with CKD; (2) compare between HD-dependent CKD patients and pre-dialysis CKD patients in terms of the treatment-related burden and HR-QOL and; (3) investigate the relationship between CKD patients' characteristics and treatment burden as well as HR-QOL.

Methods

Study design and population

A prospective, cross-sectional study was conducted to assess treatment-related burden and QOL among patients with CKD attending a kidney center in Qatar. The study population included patients diagnosed with CKD who were followed regularly for the management of the disease, its associated complications and comorbidities. This included ESRD patients receiving HD and pre-dialysis patients. Data were collected from June 2017 to November 2017.

Study setting

This study was conducted at the Fahad Bin Jassim Kidney Center, a member of Hamad Medical Corporation (HMC). This kidney center, located in Doha, is a governmental institution that provides services to Qatari citizens and residents. The center provides the following services: in-center ambulatory HD, home HD, peritoneal dialysis, outpatient services for CKD patients, and patient preparation for renal replacement therapy. Dialysis services are provided six days per week from 6:00 a.m. to 10:00 p.m. It is the main kidney center in Qatar for both dialysis and pre-dialysis (over 50% of all patients in Qatar).

Eligibility criteria

Eligibility criteria for HD and pre-dialysis patients enrolled in the study were as follows: (1) adult patients diagnosed with ESRD receiving HD treatment at Fahad Bin Jassim Kidney Centre for at least two months; (2) pre-dialysis patients who had creatinine clearance of less than 25 mL/min and were followed at a low clearance clinic. Patients receiving dialysis for at least two months were enrolled in the dialysis group to ensure that the effect of dialysis on treatment burden and HR-QoL was accounted for. Mentally-ill, dementia and unconscious patients (unable to provide consent) were excluded.

Sample and sampling technique

A sample size was calculated using a cross-sectional study sample size calculation technique with a 95% confidence level and 5% margin of error.[39] The minimum effective sample size required was 288 patients with CKD. The sample of the whole population of patients with CKD was based on the total number and distribution of patients at Fahad Bin Jassim Kidney Center (HD = 533, Low Clearance Clinic (LCC)/pre-dialysis = 180; Total = 713). The proportions of HD and pre-dialysis

patients were 75% and 25%, respectively. Thus, the number needed in each category based on the calculated proportions was 216 HD patients and 72 pre-dialysis patients, respectively. Participants were enrolled in the study using a non-probability convenience sampling technique. Potential participants attending the clinics who fulfilled the eligibility criteria were sequentially approached and those who declined were excluded from the study.

Study instruments

Treatment Burden Questionnaire (TBQ): TBQ is a questionnaire for assessment of treatment-related burden that was originally developed in French in 2012 and later translated into English.[38,40] The instrument was designed to measure treatment burden associated with multiple chronic conditions. It is composed of 15 items that assess the following domains: difficulties associated with taking medicine, self-monitoring, adapting to a certain lifestyle, keeping up with laboratory tests, doctors' appointments, social life, and organization and administrative burden. The five dimensions of TBQ are: medication burden, administrative burden, financial burden, lifestyle change burden, and social burden. The instrument responses are rated using a Likert-type scale ranging from 0 (not a problem) to 10 (a big problem). TBQ global score is generated through summation of each item score to a maximum score of 150 points.[38,40] TBQ global score are further categorized as low burden (0–50), moderate burden (51–99), and high burden (100–150).

Kidney Disease Quality of Life (KDQOL™) Questionnaire: KDQOL™ is a disease-specific QOL questionnaire that was developed in 1994 to measure HR-QOL in patients with CKD.[41] The 36-item KDQOL-36™ is a modified version of the former questionnaire that now consists of 12 generic items (SF-12) and 24 CKD-specific items.[42] The 24 disease specific items are classified as follows: burden of kidney disease (4 items), symptoms of CKD (12 items), and effect of CKD (8 items).[43] The overall KDQOL-36™ instrument consists of five dimensions: Physical Component Summary (PCS), Mental Component Summary (MCS), Burdens of Kidney Disease (BKD), Symptoms and Problems of Kidney Disease (SPKD), and Effects of Kidney Disease (EKD). The scoring procedure of KDQOL-36™ instrument followed the previous developed instrument KDQOLSF™ version 1.3 [44]. This required to transform all the numeric items to a value ranging from (0–100) points. The range of possible scores are from 0 to maximum score of 3600 with higher transformed score always indicating better QOL.[44]

Linguistic validation and cultural adaptation were conducted based on the principles of good practice for patient reported outcomes (PRO) developed by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR).[45] The nine steps that were performed in the translation and linguistic validation of the TBQ and the KDQOL-36™ are shown in Fig. 1. Therefore, contextualization and cross-cultural adaptation of the two questionnaires to the local Arabic setting of Qatar was considered during the translation process. However, no further psychometric testing was conducted.

Data collection method

Eligible patients were identified through a list compiled on a routine-basis by a nurse researcher. Two interviewers (an MSc student and a nurse researcher) administered the 15-item TBQ and the 36-item KDQOL-36™ for each eligible participant who consented to participate in the study. In addition, some demographic information (e.g. monthly income, marital status, employment status, and nationality) was also collected from the participants. The questionnaire administration was conducted using face-to-face structured interviews in a quiet room within the study center. The data collection process lasted for 15–20 min on average.
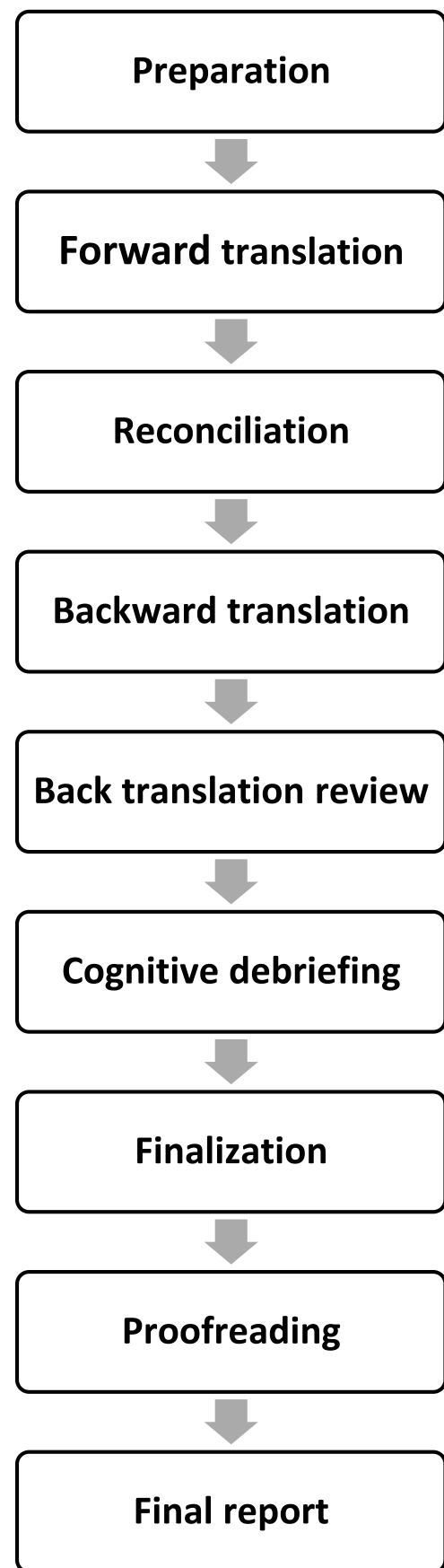

Fig. 1. International Society for Pharmacoeconomics and Outcomes Research (ISOP) steps of translation and cultural adaptation.

Statistical analysis

All data were analyzed using Statistical Package for Social Sciences, version 24 (IBM SPSS® Statistics for Windows; IBM Corp, Armonk, New York, USA). At first, normality tests were conducted for all the study continuous variables to inform selection of appropriate and robust statistical tests for treatment burden and QOL. Normality tests were conducted using Shapiro-Wilk test and Kolmogorov- Simonov (K–S) test for all the study continuous variables. Description of the study participants (sociodemographic characteristics, clinical characteristics, co-morbidities and complications, chronic medications, and pill burden) was performed through descriptive statistics using frequencies and median interquartile range (IQR) to describe the variables, and to express the treatment-related burden and perceived QOL. Inferential statistics were applied to determine the differences of the study participants comparing HD and pre-dialysis groups using Mann-Whitney and Kruskal-Wallis tests. The differences of the study variables were also assessed in relation to treatment burden and QOL using Mann-Whitney and Kruskal-Wallis tests. In order to assess the relationship between treatment-related burden and perceived QOL, correlation analysis was conducted. At first, Spearman's rank-ordered correlation test was conducted across the different study variables against the treatment burden. Second, the treatment burden was correlated against both the total perceived QOL and the five dimensions of the QOL (PCS, MSC, burden of kidney disease, symptoms/problems, and effect of kidney disease).

Ethics approval

Ethical approval for the conduct of the study was obtained from the Medical Research Center (MRC) of the HMC (approval # 16364/16). This study did not involve any medical intervention or invasive procedures; therefore, there were no foreseeable risks to the participants. Informed consent was obtained from each participant before enrolment in the study. All data were anonymously collected and were kept under lock and key by the principal investigator. No findings which could identify any individual participant will be published in this study.

Results

Response rate

Of the 460 eligible patients (HD = 380 and pre-dialysis = 80) approached, 280 (HD = 223 and pre-dialysis = 57) consented to participate in the study (response rate 60.9%). We approached 460 potential participants compared to our target of 288, because several patients declined to participate. There were no missing or invalid data, since all responses were collected through an interviewer-administered technique. All the 280 patients' responses were included in the data analyses. Data related to sociodemographic characteristics, clinical characteristics, and pill burden were obtained from the electronic health record available at HMC (i.e. CERNER) and directly from the patients wherever necessary.

Sociodemographic characteristics of the study participants

A summary of the CKD patients' sociodemographic characteristics is presented in Table 1. The median (IQR) age of the study participants was 59 (19) years. More than half of them were male (54.6%) and Qatari (54.6%). Furthermore, around 32.1% of the participants had no formal education, while 39.3% were unemployed. There were statistically significant differences between the two groups (i.e. HD group with CrCl <15 mL/min vs. pre-dialysis group with CrCl <25 mL/min) in terms of their nationality, marital status, educational level, employment status, and income per month. Pre-dialysis patients were more educated compared to HD patients (45.6% vs. 24.2% university/college graduates, respectively; p = 0.006). In addition, more than half of the pre-

Table 1
Sociodemographic characteristics of patients with CKD in Qatar.

Variable	Total	HD	Pre-dialysis	P value
	(N = 280)	(n = 223)	(n = 57)	
Median (IQR)				
Age	59 (19)	60 (20)	55 (18)	0.24
		n (%)		
Gender				
Male	153 (54.6)	120 (53.8)	33 (57.9)	0.581
Female	127 (45.4)	103 (46.2)	24 (42.1)	
Nationality				
Qatari	153 (54.6)	140 (62.8)	13 (22.8)	<0.001
Non-Qatari	127 (45.4)	83 (37.2)	44 (77.2)	
Marital status				
Married	189 (67.5)	142 (63.7)	47 (82.5)	0.034
Single	41 (14.6)	35 (15.7)	6 (10.5)	
Divorced	14 (5)	14 (6.3)	0 (0)	
Widow	36 (12.9)	32 (14.3)	4 (7)	
Educational level				
No education	90 (32.1)	72 (32.3)	18 (31.6)	0.006
Primary	25 (8.9)	23 (10.3)	2 (3.5)	
Secondary	85 (30.4)	74 (33.2)	11 (19.3)	
College/University	80 (28.6)	54 (24.2)	26 (45.6)	
Employment status				
Unemployed	110 (39.3)	92 (41.3)	18 (31.6)	<0.001
Employed	88 (31.4)	56 (25.1)	32 (56.1)	
Retired	82 (29.3)	75 (33.6)	7 (12.3)	
Income per month (QR)				
No income	63 (22.5)	46 (20.6)	17 (29.8)	<0.001
Less than 1000	3 (1.1)	1 (0.4)	2 (3.5)	
1001–5000	11 (3.9)	6 (2.7)	5 (8.81)	
5001–10,000	68 (24.3)	58 (26)	10 (17.5)	
10,001–15,000	25 (8.9)	18 (8.1)	7 (12.3)	
15,001–20,000	65 (23.2)	60 (26.9)	5 (8.81)	
20,001–25,000	23 (8.2)	20 (9)	3 (5.3)	
25,001–30,000	15 (5.4)	12 (5.4)	3 (5.3)	
More than 30,000	7 (2.5)	2 (0.9)	5 (8.8)	
Smoking status				
Never smoker	215 (76.8)	172 (77.1)	43 (75.4)	0.722
Former smoker	51 (18.2)	39 (17.5)	12 (21.1)	
Current smoker	14 (5)	12 (5.4)	2 (3.5)	

*Mann – Whitney U test; **Pearson's chi-squared (X^2) test.

dialysis patients were employed, while the majority of the HD patients were unemployed or retired (p < 0.001). More data about the comparison of HD and pre-dialysis groups in terms of their sociodemographic characteristics are presented in Table 1.

Clinical characteristics and Co-morbidities of the study participants

Most of the HD and the pre-dialysis patients were categorized as stage 5 CKD patients (99.6% vs. 78.9%, respectively; P < 0.001). The median (IQR) of the dialysis duration in HD patients was 3.1 (4.8) years, whereas the CKD duration in pre-dialysis patients was 2 (4) years. HD patients compared with pre-dialysis patients had statistically significant (but not clinically important) higher levels of hemoglobin, albumin, hematocrit, ferritin, parathyroid hormone, serum bicarbonate and potassium. The median Kt/V for HD patients was 1.7 (0.44), while the median creatinine for pre-dialysis patients was 301 (460) μmol/L [eGFR 11 (5.5) mL/min/1.73 m^2].

In general, CKD patients (n = 280) had a median (IQR) of 3 (2) chronic medical conditions. HD patients reported significantly higher number of chronic medical conditions compared to pre-dialysis patients [(3 (2) vs. 2 (3); p < 0.001]. The most prevalent chronic medical conditions were hypertension (94.6%) and diabetes (67.5%). Similarly, the prevalence of hypertension and cardiac diseases was significantly higher among HD patients compared to pre-dialysis patients (p < 0.005). Other information related to co-morbidities of the studied population is presented in Table 2.

Table 2
Co-morbidities of patients with CKD in Qatar.

Variable	Total	HD	Pre-dialysis	P value
	(N = 280)	(n = 223)	(n = 57)	
Median (IQR)				
Number of comorbidities	3 (2)	3 (2)	2 (3)	< 0.001
		n (%)		
Diabetes				
No	91 (32.5)	66 (29.6)	25 (43.9)	0.066**
Type 1	16 (5.7)	15 (6.7)	1 (1.8)	
Type 2	173 (61.8)	142 (63.7)	31 (54.4)	
Eye disease				
No	220 (78.6)	170 (76.2)	50 (87.7)	0.075**
Retinopathy	36 (12.9)	29 (13)	7 (12.3)	
Blindness	6 (2.1)	6 (2.7)	0 (0)	
Others	18 (6.4)	18 (8.1)	0 (0)	
Hypertension				
No	15 (5.4)	5 (2.2)	10 (17.5)	< 0.001
Yes	265 (94.6)	218 (97.8)	47 (82.5)	
Viral infection				
No	250 (89.3)	196 (87.9)	54 (94.7)	0.307**
HBV	6 (2.1)	4 (1.8)	2 (3.5)	
HCV	19 (6.8)	18 (8.1)	1 (1.8)	
HIV	2 (0.7)	2 (0.9)	0 (0)	
Others	3 (1.1)	3 (1.3)	0 (0)	
Liver disease				
No	269 (96.1)	212 (95.1)	57 (100)	0.231**
Cirrhosis	2 (0.7)	2 (0.9)	0 (0)	
Others	9 (3.2)	9 (4)	0 (0)	
GIT disease				
No	260 (92.9)	205 (91.9)	55 (96.5)	0.265**
Bleeding	10 (3.6)	8 (3.6)	2 (3.5)	
Others	10 (3.2)	10 (4.5)	0 (0)	
Dyslipidaemia				
No	178 (63.6)	141 (63.2)	37 (64.9)	0.814
Yes	102 (36.4)	82 (36.8)	20 (35.1)	
Cardiac disease				
No	165 (58.9)	126 (56.5)	39 (68.4)	0.005**
CAD	60 (21.4)	42 (18.8)	18 (31.6)	
Angina	1 (0.4)	1 (0.4)	0 (0)	
Cardiomyopathy	6 (2.1)	6 (2.7)	0 (0)	
Heart failure	4 (1.4)	4 (1.8)	0 (0)	
Valvular heart disease	2 (0.7)	2 (0.9)	0 (0)	
Others	42 (15)	42 (18.8)	0 (0)	

*Mann – Whitney U test; **Pearson's chi-squared (X^2) test.

Description of treatment burden among the participants

Perceived treatment-related burden was measured among the CKD patients using the TBQ (achievable global score ranges from 0 to 150, with a higher score indicating higher treatment burden). The participants reported a median (IQR) treatment burden global score of 40.5 (38) (Table 3). In a sub-group analysis, HD patients experienced significantly higher treatment burden compared to pre-dialysis patients with a median (IQR) of 45 (36) versus 25 (33), respectively (p < 0.001). About 65% of CKD patients reported low burden (TBQ score 0–50), 33.9% reported moderate burden (TBQ score 51–99), while only 1.1% indicated high burden (TBQ score 100–150). The pre-dialysis group compared to the HD group had significantly higher proportion of patients with low burden of treatment (82.5% vs. 60.5%; p = 0.005) (Table 3).

Further analysis of the five dimensions of the treatment burden is

Table 3
Analysis of the burden of treatment among patients with CKD in Qatar.

Variable	Total	HD	Pre-dialysis	P value
	(N = 280)	(n = 223)	(n = 57)	
Median (IQR)				
TBQ global score	40.5 (38)	45 (36)	25 (33)	<0.001*
TBQ categories		n (%)		
Low burden	182 (65.0)	135 (60.5)	47 (82.5)	0.005**
Moderate burden	95 (33.9)	86 (38.6)	9 (15.8)	
High burden	3 (1.1)	2 (0.9)	1 (1.8)	

*Mann – Whitney U test; **Pearson's chi-squared (X^2) test, HD: hemodialysis.

illustrated in Table 4. Perceived treatment burden of the five dimensions is reported from the highest to the lowest score as follows: medication burden (median = 15, IQR = 25), lifestyle change burden (median = 10, IQR = 10), administrative burden (median = 8, IQR = 10), social burden (median = 0, IQR = 10), and financial burden (median = 0, IQR = 0).

Marital status, educational level, and employment status were shown

Table 4
Analysis of the five dimensions of TBQ among patients with CKD in Qatar.

Variable	Range	Median (IQR)	Mean ± SD
1. Medication burden	(0–40)	15 (25)	16.8 ± 13.3
a) The problems related to the taste, shape or size of your tablets and/or the annoyances caused by your injections		3 (10)	4.1 ± 4.2
b) Number of times you should take your medication daily		5 (10)	4.5 ± 4.1
c) The efforts you make not to forget to take your medications		3 (10)	4.3 ± 4.5
d) The necessary precautions when taking your medication		0 (9.7)	3.7 ± 4.3
2. Administrative burden	(0–60)	8 (10)	7.2 ± 7.1
a) The problems related to Lab tests and other exams (frequency, time spent and associated nuisances or inconveniences		0 (0)	0.55 ± 1.8
b) The problems related to Self-monitoring: frequency, time spent and associated nuisances or inconveniences		0 (10)	4 ± 4.6
c) The problems related to Doctor visits and other appointments: frequency and time spent for these visits and difficulties finding healthcare providers		0 (0)	1.7 ± 2.2
d) how would you rate the problems related to the difficulties you could have in your relationships with healthcare providers (for example: feeling not listened to enough or not taken seriously)		0 (0)	0.28 ± 1.3
e) The problems related to Arranging medical appointments (doctors' visits, lab tests and other exams) and reorganizing your schedule around these appointments		0 (0)	1.43 ± 3.08
f) The problems related to the administrative burden related to healthcare (for example: all you have to do for hospitalizations, reimbursements and/or obtaining social services)		0 (0)	0.19 ± 0.95
3. Financial burden	(0–10)	0 (0)	1.9 ± 3.6
a) The problems related to the financial burden associated with your healthcare		0 (0)	1.9 ± 3.6
4. Lifestyle change burden	(0–20)	10 (10)	11.33 ± 6.6
a) The problems related to the burden related to dietary changes		7 (8)	6.2 ± 4
b) The problems related to the burden related to doctors' recommendations to practice physical activity		5 (10)	5.1 ± 4.4
5. Social burden	(0–20)	0 (10)	5.25 ± 7.17
a) How does your healthcare impact your relationships with others		0 (10)	3.3 ± 4.4
b) "The need for medical healthcare on a regular basis reminds me of my health problems"		0 (0)	1.93 ± 3.6
The TBQ comprises of 15 items with each item rated on a Likert scale ranging from 0 (not a problem) to 10 (a big problem)			

to significantly influence perceived treatment-related burden. Divorced and widowed patients experienced significantly higher treatment burden compared to married and single patients (p = 0.041). Moreover, both divorced and widowed patients reported significantly similar level of treatment burden with median (IQR) global TBQ scores of 52 (27) and 52 (35), respectively. Additionally, treatment burden tends to increase as educational level decreased. Uneducated patients had the highest treatment burden [median IQR (52 (38.5)] compared to educated individuals (P < 0.001). Unemployed and retired patients expressed higher treatment burden compared to employed subjects with median (IQR) of 45 (40.7), 49.5 (34), and 27.5 (28), respectively (p < 0.001). Co-morbidities such as type 2 diabetes, blindness, and valvular heart disease resulted in significantly higher treatment burden scores compared to others. Perceived TBQ scores were as follows: type 2 diabetes 47 (40), retinopathy 46.5 (29) and valvular heart disease 79.5.

Description of health-related quality of life among the participants

The perceived median (IQR) global HR-QOL score measured using the KDQOL-36™ among the participants was 2280.6 (1096.2) compared to the maximum obtainable global score of 3600. The HD patients had significantly lower QOL compared to the pre-dialysis patients with a median (IQR) score of 2140 (1100) vs. 2930 (995); (p < 0.001), respectively. The median (IQR) scores of the KDQOL-36™ five dimensions were as follows: PCS, 175 (375); MCS, 357.5 (300); burden of kidney disease, 200 (225); symptoms/problems, 925 (300); effect of kidney disease, 600 (200). The pre-dialysis patients had significantly better QOL in all the five dimensions compared to the HD patients (Table 5).

Divorced, female, Qatari, less educated, and unemployed, with income of less than 1000 QR per month, reported significantly lower QOL compared to the other groups (p < 0.05). In addition, patients who had stage 5 CKD, type 1 diabetes, hypertension, dyslipidemia, and blindness had significantly lower QOL (p < 0.05).

Correlation between treatment burden and quality of life among the study participants

A Spearman's rank-order correlation test was used to study the relationship between the perceived treatment burden measured using the TBQ and the perceived QOL measured using the KDQOL-36™ instrument. As shown in Table 6, there was a strong, negative correlation between TBQ score and KDQOL-36™ score [rs (251) = −0.616, p < 0.001]. This indicates that the higher the treatment-related burden, the lower the patients' QOL. Further correlation analyses of the five KDQOL-

Table 5
Analysis of health-related quality of life of patients with CKD in Qatar.

Variable	Total(N = 280)	HD(n = 223)	Pre-dialysis(n = 57)	P value*
Median (IQR)				
KDQOL-36™ global score				
	2280.6 (1096.2)	2140 (1100)	2930 (995)	**<0.001**
Five domains of KDQOL-36™ instrument scores				
1. PCS	175 (375)	100 (300)	400 (312.5)	**<0.001**
2. MCS	357.5 (300)	330 (315)	460 (237.5)	**<0.001**
3. Burden of CKD	200 (225)	200.7 (225)	300 (212.5)	**<0.001**
4. Symptoms/ problems	925 (300)	900 (300)	1100 (275)	**<0.001**
5. Effect of kidney disease	600 (200)	600 (175)	725 (187.5)	**<0.001**

*Mann – Whitney *U* test was applied; Maximum obtainable global score of KDQOL-36™ is 3600.
CKD: chronic kidney disease; HD: hemodialysis; MCS: Mental Component Summary; PCS: Physical Component Summary.

Table 6
Correlation between TBQ and KDQOL-36™instrument among patients with CKD in Qatar.

TBQ score		
Variable	Correlation co-efficient	P value*
Overall QOL score		
KDQOL-36™	−0.616	<0.001
Five domains of the KDQOL-36™		
1. PCS	−0.613	<0.001
2. MCS	−0.500	<0.001
3. Burden of kidney disease	−0.467	<0.001
4. Symptoms/problems	−0.468	<0.001
5. Effect of kidney disease	−0.464	<0.001

*All correlation analyses were conducted using Spearman's rho test.

36™ domains were also conducted. All the five dimensions of QOL showed statistically significant negative correlations with treatment burden. For PCS domain, there was a strong, negative correlation, with rs (251) = 0.613, P < 0.001. This indicates that, the higher the perceived treatment burden, the lower the QOL. Similarly, the other four domains (MCS, burden of kidney disease, symptoms/problems, and effect of kidney disease), resulted in moderate negative correlation with TBQ (p < 0.001).

Discussion

The concept of treatment burden starts to gain greater attention in the past few years. Despite previous attempts toward clarifying the concept of treatment burden, the principle of measuring it is not well-established. A recent systematic review highlighted that there is a significant variation in the process of how treatment-related burden is being measured.[46] Thus, there is much work needed to be done to effectively measure treatment burden in chronic medical conditions. To our knowledge, this study is the first published study to measure treatment-related burden among HD and pre-dialysis CKD patients using the TBQ. Our findings suggest that a substantial proportion (more than one-third) of the CKD patients reported moderate to high treatment-related burden. Further, the HD patients experienced significantly higher treatment burden compared to the pre-dialysis patients with medication burden and lifestyle changes burden exhibiting the highest perceived treatment-related burden. Similarly, the HD patients reported significantly lower HR-QOL compared to the pre-dialysis patients, and there was a strong negative correlation between burden of treatment and HR-QOL, signifying that HR-QOL decreases as treatment burden increases. A recent meta-analysis by Roberti et al. highlighted that being a person with ESRD always implied high burden, time-consuming, invasive and exhausting tasks, impacting on all aspects of patients' and caregivers' lives, but the investigators recommended further research in that specific area.[26]

Treatment-related burden was higher in CKD patients with low education, divorced, widowed, unemployed, and retired. This could mean that patients with higher educational background have better understanding of their chronic disease conditions, self-care and coping skills. In addition, social status like divorce and death of a spouse could lead to emotional problems, which may ultimately increase treatment burden. This result is supported by a previous study that suggested that being employed and having family support reduced perceived treatment burden associated with chronic medical conditions.[47] Similarly, having co-morbidities such as type 2 diabetes, blindness, and valvular heart disease had resulted in significantly higher treatment burden. This finding is consistent with a previous study by Sav et al., which showed that having extra chronic conditions leads to higher perceived treatment burden.[47]

In the present study, we investigated the effect of treatment burden on CKD patients' HR-QOL. Overall, HD patients had significantly lower QOL compared to pre-dialysis patients (p < 0.001). Additionally,

patients who were divorced, female, less educated, unemployed, stage 5 CKD, having type 1 diabetes, hypertension, dyslipidemia, and blindness reported significantly lower QOL compared to their counterpart groups. This was consistent with the result reported by another study that measured QOL in HD patients using the same instrument (i.e. KDQOL-36).[48] The investigators found that HD patients who were female, older, less-educated, unemployed, with stroke or diabetes mellitus, had reported significantly lower QOL than others.[48]

To date, only a few studies that quantitatively measured treatment-related burden associated with multiple chronic conditions are available in the literature.[47] We considered the study by Sav and colleagues as the most appropriate one to compare our results with, since it measured treatment-related burden among patients with chronic diseases using the same instrument (i.e. TBQ).[47] However, treatment burden was measured across multiple chronic illnesses instead of CKD population alone. Despite that, various chronic conditions might co-exist between the two studied populations. Patients with multiple chronic conditions had global treatment burden score of about 57, indicating moderate treatment-related burden compared to low treatment burden in CKD population. The highest perceived treatment burden was as follows: financial burden, lifestyle burden, social burden, administrative burden, and medication burden.[47] The reason behind such differences might be due to the nature of the care provided, fragmented healthcare system, and economic factors. In our study, financial and administrative burden were reported to be the least compared to the other aspects of treatment burden. This might be due to the free healthcare provided to Qatari, minimal treatment-related cost for residents, and the multi-disciplinary care approach at Fahad Bin Jassim Kidney Centre.

The field of treatment burden is still evolving, especially in CKD population. Future studies should utilize longitudinal study designs with a focus on CKD population who have diverse socio-demographic characteristics and cultural differences. Pharmacists can play a role in minimizing inappropriate polypharmacy and medication-related burden among CKD patients through designing effective intervention strategies such as pharmacist-led home medication reviews and intervention to improve adherence. This may potentially improve HR-QOL, save costs, and improve outcomes of care in patients with CKD in Qatar and globally. Therefore, future studies can examine the role of clinical pharmacist in decreasing medication-related burden associated with CKD patients.

Strengths and limitations

This study is the first one to investigate treatment-related burden among CKD patients in Qatar and the Middle East region using a validated quantitative tool (i.e. the TBQ) and approach. Second, the burden of treatment was related to an important and globally recognized patient-reported outcome (i.e. HR-QOL), measured using a validated disease-specific instrument (i.e. KDQOL-36™). On the other hand, this study has several limitations that need to be acknowledged. First, it was cross-sectional in nature and captured treatment-related burden at a single point in time. Longitudinal study design may be more appropriate to examine the relationship between treatment-related burden and other factors as well as possible changes over time in CKD patients. Second, a convenience sampling technique was used instead of a more robust probability sampling technique due to the following reasons: 1) the nature of pre-dialysis patients' state and the unpredicted deterioration across the disease state, and 2) the variety of discomfort expressed by HD patients that is related to their HD including preparations for catheter insertion, hypotension, and dizziness, warranted recruiting them conveniently. Thus, convenience sampling was more appropriate. However, we do acknowledge that we might have omitted the most severe cases of CKD with highest perceived treatment-related burden leading to unrepresentative study sample. In addition, the convenience sampling approach might have resulted in the recruitment of a

disproportionately large proportion of Qatari participants compared to the actual population in the country (55% vs. <15%). Therefore, the findings cannot be generalized to the entire population of Qatar. Similarly, since the majority of the patients (95%) were CKD stage 5, the results may not be generalizable to the entire CKD patients population in Qatar. Third, some socio-demographic variables such as smoking and other variables like CKD duration were collected directly from the CKD patients, which were subject to social desirability and recall bias. Fourth, this study was restricted to CKD patients who could speak Arabic and/or English only. Thus, treatment-related burden may not be generalized to other cultures or countries. This could be the most significant drawback of the current study, since the state of Qatar has one of the most diverse cultures. Furthermore, quantitative data collection using TBQ and KDQOL-36™ was through interviewer administration approach that may result in social desirability bias. However, during each interview, the researcher restrict herself to the interview protocol and avoided any personal knowledge, beliefs and influences.

Conclusion

A considerable proportion of CKD patients suffered from treatment-related burden and deterioration in HR-QOL at a varying degree of seriousness. Marital status, educational level, employment status, co-morbidities such as type 2 diabetes, blindness, and valvular heart disease, were all factors that significantly lead to higher perceived treatment burden. Additionally, there were a number of strong and moderate correlations between the TBQ score and the five dimensions of KDQOL-36™, which indicates higher treatment-related burden is associated with lower patients' HR-QOL. Our study suggests that treatment-related burden should be taken into account in CKD management strategies. Moreover, previously identified factors that increase treatment-related burden should be considered when designing healthcare interventions directed toward CKD population.

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Declaration of competing interest

The authors declare that they have no conflict of interest.

Ethics approval

Ethical approval for the conduct of the study was obtained from the Medical Research Center (MRC) of the HMC (approval # 16364/16). Informed consent was obtained from all the participants involved in this study. All procedures performed in the study were in accordance with the good clinical practice and the Declaration of Helsinki 1964 and comparable ethical standards.

Authors' contributions

Conception of the research idea and research design: AA, AAM, FSA, AIH, MIMI, NK, RAI, MAB; data acquisition: AAM, RAI, MAB; data analysis/interpretation: AAM, AA, MIMI, NK, AIH; supervision/mentorship: MIMI, NK, AA; manuscript writing: AAM, AA, FSA, AIH, MIMI, NK, RAI, MAB. Each of the authors: has provided intellectual content of critical importance during the initial manuscript draft and manuscript revision; approves the submitted version of the manuscript and; accepts personal accountability for the content of the paper and author's own contributions.

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