Comparing prevalent symptoms in advanced chronic kidney disease and chronic kidney disease after a failed kidney transplant

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ABSTRACT

Background: Patients with advanced chronic kidney disease (CKD) experience a high burden of symptoms comparable to cancer patients. Symptoms vary widely depending on age and comorbidities and tolerance thresholds. Complaints include symptoms related to uremic toxins accumulation and reduced urine output. There is also a failed transplant population with advanced CKD (CKD-T).

Objective: This study aims to compare symptom burden between advanced CKD and CKD after a failed kidney transplant (CKD-T).

Patients and methods: This cross-sectional study included fifty advanced CKD patients with glomerular filtration rate (GFR) less than 30 ml/min /1.73m^2 and fifty advanced CKD patients GFR less than 30 ml/min/1.73m2 after a failed kidney transplant (CKD-T) from Ain Shams University Outpatient Nephrology Clinic and a Private Nephrology Clinic. Patients were adults older than 18 years. Patients who agreed to participate were given CHOICE questionnaire for uremic symptoms.

Results: The mean age of the CKD group was 47.9 ± 14.3 compared to 52.3± 8.9 years for CKD-T. Fifty percent of the groups were males. Sixty six percent had hypertension in the CKD group compared to 70 % in CKD-T group. Cardiovascular disease was 60 % in the CKD-T group and only 32 % in CKD group. In the CKD group 32 % had diabetes compared to 46 % in the other group. Only 12% of patients had an arteriovenous fistula (AVF) in CKD and 4% of CKD. Hospitalization with infection in the past two years was 13.3% in the CKD 45% in the CKD -T group<0.04. Mean urea level was 91.7 ± 12.3 in the CKD group and 84.9 ± 16.8 mg/dl in the CKD-T, p<0.035. Mean creatinine was similar in both groups 4.8 ± 0.4 in CKD group and 4.9 ± 0.3 mg/dl, p= 0.3. Fatigue was present in 73% of CKD and 70 % in CKD-T. Anorexia was encountered more in the CKD group 53 % and 45 % but this difference was not statistically significant p 0.6. Trouble sleeping was a frequent complaint in the CKD 70% as opposed to 44% in CKD-T. More patients complained of shortness of breath in CKD-T 66% versus 34 % in CKD with p <0.03. More patients in CKD group complained of reduced urine output (47%) but with no statistical significance p 0.2. Cramps and bone pain were equal in both groups. Lower limb edema was more prevalent 80 % in CKD and 60 % in CKD-T with various degrees.

Conclusion: CKD symptoms were comparable between the two groups. CKD-T patients experienced a symptom burden comparable to CKD patients. Shortness of breath was more prevalent in the CKD-T group. Fatigue and nausea were associated with age more than 50 and urea level>80 mg/dl.

Keywords: Chronic kidney disease, Failed kidney transplant.

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INTRODUCTION

Chronic kidney disease (CKD) is a progressive disorder that affects more than 10% of the world's population, or over 800 million people. It has emerged as one of the world's major causes of mortality, particularly in the last two decades. It imposes a substantial economic burden in low-income nations [(1)]. Patients with advanced CKD experience a high burden of symptoms comparable to cancer patients [(2)].

Symptoms vary widely depending on age, comorbidities and tolerance thresholds. CKD symptoms are related to uremic toxins accumulation and reduced urine output. Uremic symptoms contribute significantly to the low quality of life experienced by CKD patients. To stratify this group of patients, the National Kidney Foundation (NFK) issued clinical practice guidelines and recommendations based on a five-stage categorization of CKD based on renal function [(3)].

Kidney transplant recipients are a distinct group of patients with high rates of morbidity and death, and they are classified as having CKD regardless of glomerular filtration rate (GFR) or the presence or absence of kidney damage indicators [(4)]. As we are transplanting more patients, the population of patients with a failed kidney transplant has grown. Whether the prevalence or intensity of uremic symptoms are different in advanced CKD from CKD T is not known. This study aims to compare symptom burden between the two groups.

PATIENTS AND METHODS

This cross-sectional study included 50 non dialysis CKD patients with glomerular filtration rate (GFR) <30 ml/min/1.73 m^2 and 50 CKD patients with GFR < 30 ml/min/m2 after a failed kidney transplant (CKD-T). Patients were enrolled from Ain shams university outpatient nephrology clinic and a private nephrology clinic. Patients were adults older than 18 years. Patients who agreed to participate were given a questionnaire about CKD symptoms. We used The CHOICE Health Experience Questionnaire to assess uremic symptoms. We excluded patients with active infection or malignancy.

History and examination were documented. Blood tests on the day including Full blood count (FBC), Kidney function tests (Creatinine, Urea) and Electrolytes (Sodium, potassium, Calcium) and parathyroid hormone (PTH) were recorded and analysed.

Ethical approval:

The study was authorised by Ain Shams University's Faculty of Medicine Ethics Committee. Each participant received a full summary of the study's aims prior to completing an informed consent form.

Statistical analysis:

IBM SPSS Software Package Version 20.0 was used to analyse the data that were supplied into the computer. Numbers and percentages were used to represent categorical data. The X^2-test was used to evaluate differences between two groups. Alternatively, when more than 20% of the cells had an anticipated count of less than 5, the Fisher Exact adjustment test was used. The Shapiro-Wilk test was used to determine if the continuous data were normal. The following were used to express quantitative data: mean±standard deviation, median, and range (lowest and highest). When comparing two groups of regularly distributed quantitative data, the student t-test was employed, whereas the Mann-Whitney test was utilised when comparing two groups of non-normally distributed quantitative

variables. A significant p-value was defined as equal to or less than 0.05.

Results

The mean age of the CKD group was 47.9 ± 14.3 compared to 52.3± 8.9 years for CKD-T. Fifty percent of the groups were males. Sixty six percent had hypertension in the CKD group compared to 70 % in CKD-T group. Cardiovascular disease included ischemic heart diseases and heart failure and rhythm abnormalities was 60 % in the CKD-T group and only 32 % in CKD group. In the CKD group 32 % had diabetes compared to 46 % in the other group. Only 12% of patients had an arteriovenous fistula (AVF) in CKD and 4% of CKD. Hospitalization with infection in the past two years was 13.3% in the CKD 45% in the CKD -T group<0.04.

Mean urea level was 91.7 ± 12.3 in the CKD group and 84.9 ± 16.8 mg/dl in the CKD-T, p<0.035. Mean creatinine was similar in both groups 4.8 ± 0.4 in CKD group and 4.9 ± 0.3 mg/dl, p= 0.3.

Potassium mean was higher 5.1 in CKD compared to 4.7 in CKD-T, p 0.03. Haemoglobin was similar in both groups median 9 mg/dl in CKD and 9.3 mg/dl in CKD T. There was no significant difference in sodium or calcium levels in the two groups. Mean parathyroid hormone levels was 150 ± 20.3 compared to 153 ± 18.6pg/ml in the CKD -T group as shown in table (1).

Table (1): Comparison between the two studied groups according to different parameters

	CKD (n = 50)	**CKD-T (n = 50)**	**Test of Sig.**	**p**
Age years, mean (SD)	**47.9 ± 14.3**	**52.3 ± 8.9**	**U=267.50**	**0.519**
Male	**25 (50%)**	**25 (50%)**	**χ^2=0.000**	**1.000**
Clinical characteristics				
Diabetes	**16 (32%)**	**23 (46%)**	**χ^2=093**	**0.405**
Hypertension	**33 (66%)**	**35 (70%)**	**χ^2=0.061**	**0.804**
Cardiovascular disease	**16 (32%)**	**30 (60%)**	**χ^2=8.333***	**0.007***
Arteriovenous fistula	**6 (12%)**	**2 (4%)**		
Hospitalization with infection in the past two years	**6 (13.3%)**	**22 (45%)**		**0.04**
Blood chemistry				
Urea(mg/dl) mean, (SD)	**91.7(12.3)**	**84.9(16.8)**	**U=193.50***	**0.035***
Creatinine(mg/dl) mean, (SD)	**4.8(0.4)**	**4.9(0.3)**	**t=0.938**	**0.35**
Sodium (meq/l) mean, (SD)	**138.4(4.7)**	**137.9(4.3)**	**t=0.444**	**0.659**
Potassium(meq/l)mean, (SD)	**5.1(0.5)**	**4.7(0.6)**	**U=191.5**	**0.031***
Haemoglobin(g/dl)mean, (SD)	**9(1.1)**	**9.3(0.6)**	**t=1.039**	**0.304**
Calcium(mg/dl) mean, (SD)	**8.6(0.6)**	**8.3(0.7)**	**t=1.741**	**0.088**
PTH (pg/ml) mean, (SD)	**150(20.3)**	**153(18.6)**		**0.6**

SD: Standard deviation, t: Student t-test, U: Mann Whitney test, χ^2: Chi square test

*: Statistically significant at $p \leq 0.05$

In table (2) Prevalence of CKD symptoms was compared between the two groups CKD and CKD-T. Fatigue was present in 73% of CKD and 70 % in CKD-T. Anorexia was encountered more in the CKD group 53 % and 45 % but this difference was not statistically significant p 0.6. Trouble sleeping was a frequent complaint in the CKD 70% as opposed to 44% in CKD-T. More patients complained of shortness of breath in CKD-T 66% versus 34 % in CKD with p <0.03.More patients in CKD group complained of reduced urine output (47%) but with no statistical

significance p 0.2. Cramps and bone pain were equal in both groups.Lower limb edema was more prevalent 80 % in CKD and 60 % in CKD-T with various degrees.

Table (2): Comparison between the two studied groups according to CKD symptoms

CKD symptoms	CKD (n = 50)	CKD -T (n = 50)	Test of Sig.	p
Fatigue	36 (73.3%)	35 (70%)	0.066	0.797
Anorexia	26 (53.3%)	22 (45%)	0.333	0.564
Nausea	28 (56%)	22(45%)	0.654	0.419
Vomiting	16 (32%)	5(10%)	3.582	0.091
Itching	6 (12 %)	5 (10%)	0.397	0.529
Trouble sleeping	35 (70%)	22 (44%)	3.125	0.077
Difficulty concentrating	34 (68%)	30 (60%)	0.535	0.465
Lower limb swelling	40 (80%)	30 (60%)	2.381	0.123
Shortness of Breath	17 (34%)	33 (66%)	4.844	0.028*
Reduced amount of urine	23 (46.7%)	15 (30%)	1.624	0.203
Cramps	10 (20%)	10 (20%)	0.000	FEp=1.000
Bone pain	16 (33.3%)	15 (30%)	0.061	0.804
Diarrhoea	8 (16%)	8 (16%)	0.028	FEp=1.000
Constipation	11 (23.3%)	20 (40%)	1.587	0.208
Low mood	12 (24 %)	22 (44%)		0.04

χ^2: Chi square test FE: Fisher Exact

*: Statistically significant at $p \leq 0.05$

In table (3) Fatigue was associated with patients older than 50 yrs, p 0.02 more than diabetes and urea level> 80 mg/dL. There was also a correlation between age older than 50 and nausea p <0.013 but not with urea level or Diabetes as shown in table (4).

Table (3): Univariate logistic regression analysis for different parameters affecting fatigue

	Fatigue		Univariate	
	No	Yes	OR (LL – UL 95%C.I)	p
Age				
≤50	10(71.4%)	12(33.3%)		
>50	4(28.6%)	24(66.7%)	5.0(1.295 – 19.303)	0.020*
DM				
No	14(100%)	17(47.2%)		
Yes	0(0%)	19(52.8%)	–	0.998
Urea (mg/dl)				
Urea>80			1.034(0.988 – 1.081)	0.15

OR: Odd`s ratio, C.I: Confidence interval, LL: Lower limit, UL: Upper Limit

p: p value for Odd`s ratio for comparing between the studied groups

*: Statistically significant at $p \leq 0.05$

Table (4): Univariate logistic regression analysis for different parameters affecting nausea

	Nausea		Univariate	
	No (n = 24)	**Yes (n = 26)**	**OR (LL – UL 95%C.I)**	**p**
Age				
≤50	15(62.5%)	7(26.9%)		
>50	9(37.5%)	19(73.1%)	4.524(1.366 – 14.981)	0.013*
DM				
No	24(100%)	7(26.9%)		
Yes	0(0%)	19(73.1%)	–	0.998
Urea>80 mg/dl			1.03(0.9-1.08)	0.83

OR: Odd`s ratio, C.I: Confidence interval, LL: Lower limit, UL: Upper Limit

*: Statistically significant at $p \leq 0.05$

There was no association between bone pain and calcium level<8 mg/dl OR 3.375(0.904 – 12.6) CI 95% P< 0.4 also no association between urea more than 80 mg/dl and bone pain as shown in table (5). Shortness of breath was associated with cardiovascular disease presence p<0.05 and urea>80 mg/dl (0.86-0.96) p<0.002 but not hemoglobin <9 g/dl OR 0.85 (0.63-0.96) p 0.64 as shown in table (6).

Table (5): Univariate logistic regression analysis for different parameters affecting Bone pain

	Bone Pain		Univariate	
	No (n = 34)	**Yes (n = 16)**	**OR (LL – UL) 95%C.I**	**p**
Urea (mg/dl)				
Mean ± SD.	77.5 ± 16.5	82.1 ± 8.4		
Median (Min. – Max.)	80.5(47 – 111)	80.5(70 – 100)	1.023(0.980 – 1.068)	0.302
Calcium (mg/dl)	>8	<8	1.03(0.89-1.1)	0.4

OR: Odd`s ratio, C.I: Confidence interval, LL: Lower limit, UL: Upper Limit

p: p value for Odd`s ratio for comparing between the studied groups.

*: Statistically significant at $p \leq 0.05$

Table (6): Univariate logistic regression analysis for different parameters affecting Shortness of Breath

	Shortness of Breath		Univariate	
	No (n =27)	**Yes (n =23)**	**OR (LL – UL) 95%C.I**	**p**
Cardiovascular				
No	10(37%)	15(65.2%)		
Yes	17(63%	8(34.8%)	0.314(0.098 – 1.001)	0.050*
Urea >80 mg/dl			0.92(0.86-0.96)	0.002
Hemoglobin <9 (g/dl)			0.85 (0.63-0.96)	0.64

OR: Odd`s ratio, C.I: Confidence interval, LL: Lower limit, UL: Upper Limit

*: Statistically significant at $p \leq 0.05$

DISCUSSION

Patients with early stages of CKD are asymptomatic or have mild symptoms ranging from foamy urine to nocturia. Sometimes symptoms may be related to the underlying disease like tingling and numbness in diabetic patients and dyspnoea related to underlying cardiovascular disease.

It is widely acknowledged that the main cause of CKD symptom burden is uremic toxins, but treatment of uraemia by dialysis came sometimes fail to resolve some of the symptoms. In addition, dialysis introduces other issues like pain in access sites and headaches and hypotension due to fluid shifts during treatment.

We used Choices for Health Outcomes in Caring for ESKD (CHOICE) study to describe CKD symptoms in both groups. This questionnaire is added to the supplement.

We identified patients with GFR less than 30 ml/min using the MDRD algorithm, despite significant problems in assessing GFR as a measure of CKD stage in the kidney transplant [(5)]. Both the Modification of Diet in Renal Disease research and the CKD Epidemiology Collaboration creatinine equations are unlikely to perform as well in transplanted patients as in non-transplanted individuals [(6)].

Evans et al.'s[(7)] study suggests that patients with CKD who have kidney transplants may not receive the same level of care as those who have CKD in their native kidneys and indeed in this study there were less patients with dialysis access than CKD patients. We have noticed similar blood pressure control between the two groups. Although prior studies have observed worse blood pressure control [(8)]. **Perl et al.** [(8)] used data from the DOPPS study to compare CKD patients and CKD after transplant. Mean Haemoglobin was 11.1 in the transplant group and 11.6g/dl in the transplant naiive group. In this study, anaemia was similar in both groups but both groups mean hemoglobin was 9.1 although most patients were on iron and erythropoietin injections. Same pattern was observed in a study by **Ansell et al.**[(9)] as well as worse blood parameters like lower bicarbonate levels and greater phosphate levels in patients with failed transplants compared to those with native CKD.

In this study CKD symptom burden seemed comparable in the two groups. Symptoms like fatigue, anorexia, nausea, lower limb oedema, itching and reduced urine output were more prevalent in the CKD population. Hospitalization with infection in the past 2 years was more common in the CKLD-T group with statistical significance. This is a common observation in various studies comparing the two groups. **Karuthu et al**. [(10)] concluded that infections are more common in kidney transplant recipients than in CKD patients or the general population. However, the detrimental impact of infections on transplant outcomes is improving.

We found no association between urea and bone pain, unlike **Massy et al.** [(11)] **and Parajuli et al.**[(12)] who found urea positively associated with bone or joint pain OR 1.34 $p<0.01$.

Shortness of breath was commoner in the CKD 5T group but when looking at the confounding variables, shortness of breath was found to be related to cardiovascular disease and urea > 80 mg/dl but not statistically related to haemoglobin level <9 gm/dl. The lack of association with anaemia but is possibly due to small sample size.

This study has limitations due to small sample size. This study did not include all uremic symptoms or symptoms of depression. We also don't have all data regarding and did not fulfil all uremic symptoms including depression.

CONCLUSION

CKD symptoms were comparable between the two groups. CKD-T patients experienced a symptom burden comparable to CKD patients. Shortness of breath was more prevalent in the CKD-T group. Fatigue and

nausea were associated with age more than 50 and urea level>80 mg/dl.

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