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Determinants of Drug Therapy Problems among Renal Transplant Recipients in a Tertiary Hospital in Kenya

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Data on the determinants of drug therapy problems among renal transplant recipients is scarce in resource-constrained settings. A cross-sectional study was conducted among 76 conveniently sampled renal transplant recipients at the Renal Clinic in Kenyatta National Hospital to evaluate the determinants of drug therapy problems. Drug therapy problems were identified and classified according to the internationally established guidelines. Drug therapy problems were prevalent among the patients (77.6%). The most common drug therapy problems were adverse drug reactions (60.5%), non-adherence (26.3%) and additional drug therapy needed (18.4%). Drug therapy problems were significantly associated with participants age ≥ 60 years (p=0.035), polypharmacy ≥ 9 medications (p=0.015), ≥ 3 comorbidities (p=0.011) and body mass index ≤ 18.5 (p=0.050). Results suggest that elderly patients who were underweight, with comorbidities and multiple medications require to be intensely monitored for drug therapy problems. Further longitudinal research is needed to mitigate drug therapy problems among renal transplant recipients.

Key words: Renal transplant recipients, drug therapy problems, immunosuppressive therapy

INTRODUCTION

Renal transplantation is a treatment modality for end stage renal disease (ESRD). It is associated with improved quality of life and reduced morbidity and mortality.[1] The Global Observatory on Donation and Transplantation estimated that there were 90,306 kidney transplants performed worldwide in 2017.[2] In Kenya, the number of ESRD patients who had undergone renal transplantation was 370 in 2013.[3]

According to Cipolle *et al.* a drug therapy problem (DTP) is "any undesirable event experienced by a patient that involves drug therapy that interferes with achieving desired goals of therapy."[4] Renal transplant recipients (RTRs) require life-long immunosuppressive therapy to prevent loss of the renal allograft as well as other drugs for the co-existing comorbidities.[5] This polypharmacy leads to poor adherence, drug interactions, adverse drug reactions and other DTPs.[6–8] Studies have shown that DTPs are associated with increased rates of rejection, infections, graft failure, hospitalizations and mortality in RTRs with an overall increase in the health care costs.[9,10] Therefore, identification, prevention and resolution of DTPs are essential for optimization of therapeutic outcomes and improvement of quality of life among RTRs.

Available data suggests that polypharmacy, multiple comorbidities, old age and drugs with narrow therapeutic indices are associated with DTPs.[7,11,12] However, there is scarcity of published data on DTPs and the determinants among RTRs in sub-Saharan Africa. A cross-sectional study was therefore designed with the aim of establishing the DTPs and their predictors among RTRs in a leading referral hospital in Kenya.

METHODOLOGY

A cross-sectional study was conducted among RTRs at the renal unit in Kenyatta National Hospital (KNH) between June and September 2020. The study enrolled RTRs aged 18 years and above, on at least one medication. Patients were at least 2 weeks' post-transplantation, on follow-up care at the renal unit and gave voluntary informed consent. Those RTRs who were on hemodialysis due to graft failure were excluded. A sample size of 76 participants was calculated using the Charan formula[13], and

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convenience sampling was used in the selection.

Ethical approval was sought from Kenyatta National Hospital/University of Nairobi-Ethics and Research Committee (KNH/UoN-ERC) vide reference number P54/02/2020. Permission to carry out was also granted by the Department of Medicine at Kenyatta National Hospital (KNH) as well as National Commission for Science, Technology and Innovation (NACOSTI). Eligible patients were taken through consenting process and those who accepted to participate in the study signed the informed consent document.

Socio-demographic, clinical characteristics and medication history of the patients was collected through patient interviews and review of their medical records. DTPs were identified and classified according to *Cipolle et al*.[4] Raw data from the study questionnaires was directly entered into a MS Excel database and exported into STATA software 13.0 (StataCorp, USA) for data analysis. Continuous variables were summarized as measures of central tendency. Categorical variables such as types of DTPs were summarized as frequencies and percentages. Bivariate analysis was conducted to determine associations between the sociodemographic, clinical characteristics and DTPs using Chi-square test. Multivariate logistic regression was used to determine the strength of association between the predictor and DTPs at 95% confidence limit.

RESULTS

A total of 76 participants were enrolled, most of whom were males (n=56, 73.7%). The median age of the participants was 49 years (IQR 35.5, 58.5), with a range of 22 to 72 years. The mean duration after kidney transplantation was 59.0 (SD± 53.3) months, ranging from 4.25 to 371 months. The mean duration of CKD before transplantation was 23.6 (SD ± 14.5) months, with a range of 4 to 72 months. All transplants were living-donor kidney transplants (Table 1).

Table 1: Socio-demographic and clinical characteristics of study participants (n=76)

Variable	Category	n (%)
Sex	**Male**	**56 (73.7)**
	Female	20 (26.3)
Age (years)	20-34	17 (22.4)
	35-49	22 (28.9)
	50-64	**29 (38.2)**
	≥65	8 (10.5)
	Median [IQR]	**49.0 [35.5,58.5]**
Body Mass Index	<18.5	4 (6.5)
	18.5-24.9	**28 (45.1)**
	25-29.9	24 (38.7)
	≥30	6 (9.7)
Marital status	Single	15 (19.7)
	Married	**58 (76.3)**
	Widowed	3 (4.0)
Education	Informal	1 (1.3)
	Primary	8 (10.5)
	Secondary	29 (38.2)
	Tertiary	**38 (50.0)**
Employment	Unemployed	13 (17.1)
	Employed	27 (35.5)
	Self-employed	**29 (38.2)**
	Retired	
Monthly income (KES)	**<10000**	**28 (36.9)**
	11000-30000	18 (23.7)
	31000-50000	15 (19.7)
	>50000	15 (19.7)
Insurance	No	1 (1.3)
	Yes	**75 (98.7)**
Residence	**Rural**	**49 (64.5)**
	Urban	27 (35.5)
Cigarette smoking	**Non-smokers**	**76 (100)**
Alcohol intake	No	73 (96.1)
	Yes	3 (3.9)
Duration after transplant (months)	-	**59.0 ± 53.3**
CKD duration (months)	-	**23.6 ± 14.5**
Type of donor	Living donor	**76 (100)**

CKD - chronic kidney disease, IQR – inter-quartile range, SD - standard deviation, KES-Kenya shilling.

All participants expressed belief that the medication prescribed to them was making them feel better. Most participants had knowledge of the indication (n=73, 96%), dose (n=75, 96.6%) and frequency (n=75, 96.6%) of their medications. Forty-six (60.5%) participants felt like they were taking too many medications. Sixty-three (82.9%) participants had experienced side effects associated with their medication. Seventy-one (93.4%) reported that the cost of medication was high (Figure 1).

A total of 91 DTPs were identified among the study participants. Approximately three-quarters (n=59, 77.6%) of the participants had at least one DTP. The different categories of DTPs are shown (Figure 2). The most frequent DTP was adverse drug reactions (ADRs) (n=46, 60.5%) followed by non-adherence (n=20, 26.3%) and additional therapy needed (n=14, 18.4%).

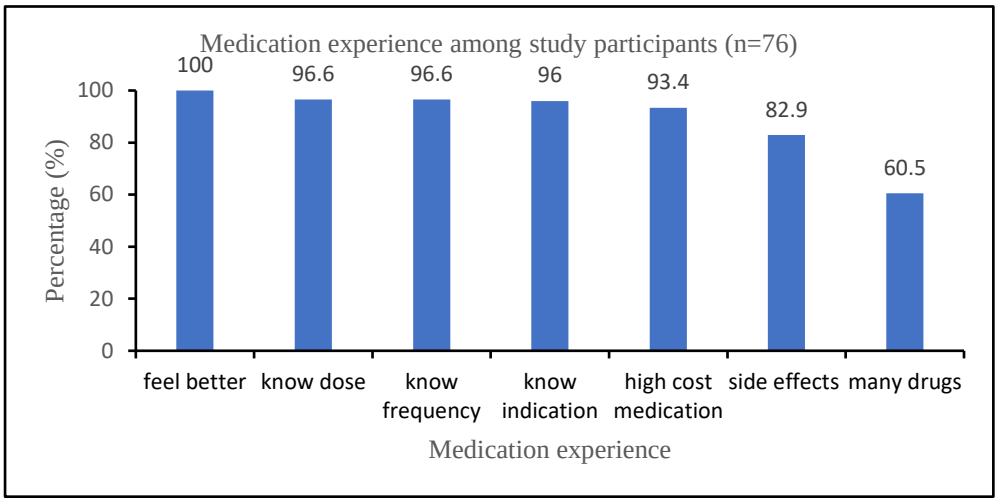

Figure 1: Medication experience among the study participants (n=76)

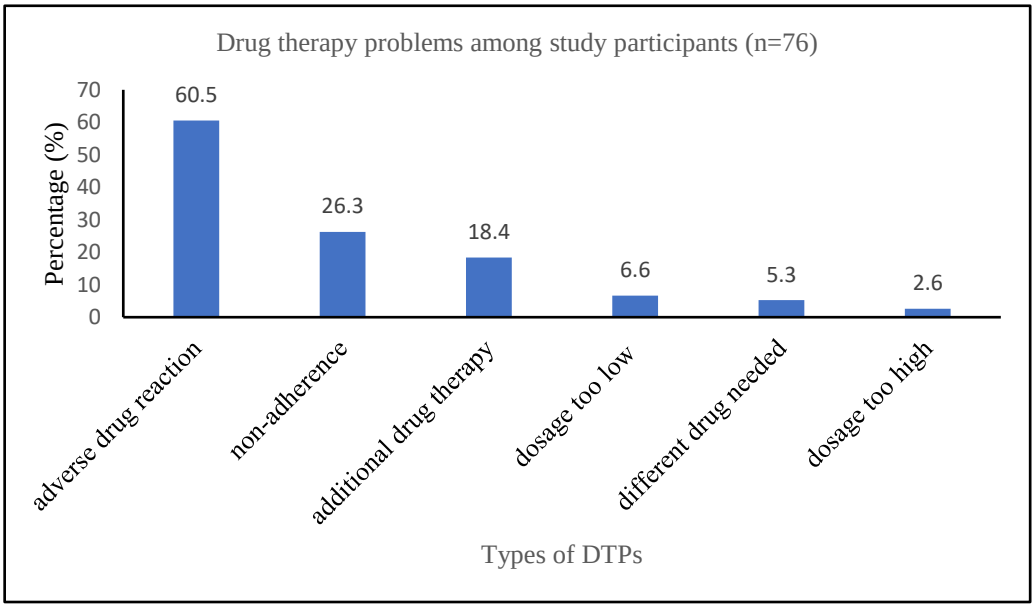

Figure 2: Drug therapy problems among study participants

Specific DTPs among study participants are highlighted in Table 2. Forty-six (60.5%) participants experienced undesirable effects as a result of the medications. The most common ADRs were flatulence, diarrhea associated with mycophenolate mofetil and tremors, associated with tacrolimus. Preventive therapy (n=10, 13.2%) was the most frequent cause of additional therapy needed, while unaffordability of drug product (n=11, 14.5%) and, forgetfulness (n=8, 10.5%) were the frequent causes of non-adherence among participants.

Table 2: Specific DTPs among study participants

DTP	n (%)
Additional therapy needed	
Preventive therapy	**10 (13.2)**
Untreated condition	3 (4.0)
Synergistic therapy	1 (1.3)
Different drug needed	
Condition refractory to the	**3 (4.0)**
drug	1 (1.3)
More effective drug available	
Dosage too low	
Additional monitoring needed	**4 (5.2)**
Ineffective dose	1 (1.3)
Adverse drug reaction	
Undesirable effect	**46 (60.5)**
Dosage too high	
Additional monitoring needed	2 (2.6)
Drug interaction	2 (2.6)
Non-adherence	
Cannot afford drug product	**11 (14.5)**
Forgetfulness	8 (10.5)
Drug product not available	1 (1.3)

The independent predictors of additional therapy need and non-adherence identified through multivariable analysis are presented in Tables 3 and 4, respectively. Age ≥60 years was independently associated with an increased likelihood of patient requiring additional therapy (aOR 20.04; 95% CI: 1.22–327.32; p = 0.035) while patients with a BMI ≤18.5 were twenty-two times more likely to be non-adherent (aOR 22.10; 95% CI: 1.03–486.80; p = 0.050). Similarly, having ≥3 comorbidities was independently associated with non-adherence (aOR 84.22; 95% CI: 2.78–2551.30; p = 0.011). In contrast, use of ≥9 medications was significantly associated with lower odds of non-adherence (aOR 0.22; 95% CI: 0.00–0.47; p = 0.015).

DISCUSSION

In this cross-sectional study involving renal transplant recipients attending follow-up care at the largest teaching and referral hospital in Eastern Africa, drug therapy problems were highly prevalent among the study participants. The most commonly identified drug therapy problems were adverse drug reactions, non-adherence, and the need for additional therapy. Furthermore, age, number of medications, presence of multiple comorbidities, and body mass index were significantly associated with the occurrence of drug therapy problems.

The prevalence of DTPs reported in this study is slightly lower than findings from USA, Canada and Brazil.[7,14,15] A possible explanation for the lower prevalence found in this study could be the inclusion of a clinical pharmacist in the multidisciplinary team at the renal clinic during follow-up visits. However, the prevalence is still high probably due to complexity of the immunosuppressive regimens, polypharmacy, and multiple comorbidities among RTRs.[9,10]

Preventive therapy needed was the leading cause of needs additional drug therapy among RTRs. Furthermore, studies have shown that vaccine preventable diseases such as influenza and pneumonia were major causes of morbidity and mortality in solid organ transplantation such as RTRs.[16] However, nearly all participants aged ≥65 years in this study had not been vaccinated against influenza and streptococcal pneumonia. This is not uncommon in the present study because several other studies have shown that the uptake of influenza and pneumococcal vaccine is low among solid organ transplant recipients.[17–19].

The Advisory Committee on Immunization Practices (ACIP) and American Society of Transplantation and Infectious diseases' guidelines recommend annual seasonal influenza and pneumococcal vaccine in addition to other vaccines in solid organ transplant recipients.[20,21].

Table 3: Multivariate logistic regression for independent correlates of needs additional therapy

	Bivariable analysis		Multivariable analysis	
Variable	**cOR (95% CI)**	**P-value**	**aOR (95% CI)**	**P-value**
Age group (years)				
20-39	1.00		1.00	
40-59	1.50 (0.25-8.88)	0.655	2.67 (0.33-21.69)	0.356
≥60	16.0 (2.67-95.75)	**0.002**	20.04 (1.22-327.31)	**0.035**
Education				
Tertiary	1.00		1.00	
Secondary	3.60 (0.84-15.45)	0.084	1.32 (0.22-7.87)	0.757
Primary	7.56 (1.34-42.63)	**0.022**	1.67 (0.17-16.49)	0.656
Employment				
Employed	1.00		1.00	
Unemployed	11.56 (1.13-117.43)	**0.039**	11.46 (0.76-173.12)	0.078
Self employed	5.42 (0.59-49.75)	0.135	2.38 (0.19-30.21)	0.503
Retired	34.67 (2.86-420.64)	**0.005**	3.29 (0.125-86.12)	0.475
Dyslipidemia				
No	1.00		1.00	
Yes	3.75 (1.02-14.06)	**0.050**	2.25 (0.39-13.10)	0.365

aOR-Adjusted Odds Ratio, CI- Confidence Interval, cOR- Crude Odds Ratio

Table 4: Multivariate logistic regression for independent correlates for non-adherence

	Bivariable analysis		Multivariable analysis	
Variable	**cOR (95% CI)**	P-value	**aOR (95% CI)**	P-value
BMI				
Normal	1.00		1.00	
underweight	14.0 (1.31- 150.01)	**0.029**	22.10 (1.03-486.8)	**0.050**
Overweight	0.92 (0.24-3.51)	0.904	0.43 (0.06-2.97)	0.394
Obese	1.75 (0.26-11.99)	0.569	0.08 (0.04-1.80)	0.115
Employment				
Employed	1.00		1.00	
Unemployed	3.0 (0.73-12.39)	0.129	4.2 (0.41-43.72)	0.266
Self employed	0.56 (0.14-2.25)	0.414	0.35 (0.04-3.18)	0.352
Retired	4.67 (0.81-26.86)	0.085	3.80 (0.20-70.61)	0.371
Number of medications				
3-5	1.00		1.00	
6-8	0.52 (0.15-1.86)	0.317	0.45 (0.68-2.93)	0.400
≥9	0.20 (0.04-1.01)	**0.050**	0.22 (0.00-0.47)	**0.015**
Number of comorbidities				
1	1.00		1.00	
2	1.11 (0.35-3.55)	0.855	5.37 (0.74-39.29)	0.098
3	2.92 (0.70-12.11)	0.140	84.22 (2.78-2551.30)	**0.011**

aOR-Adjusted Odds Ratio, BMI- Body Mass Index, CI- Confidence Interval, cOR- Crude Odds Ratio

This was, however, not the case among the study participants despite the fact that a prospective study showed that influenza vaccine was effective in reducing complications and admission to intensive care in solid organ transplant recipients.[22] Three (4.0%) participants had untreated conditions which was lower compared to 28.4% reported by Chisholm *et al.* [23]. This finding may be explained by the availability of specialists at the KNH renal unit.

In multivariate analysis old age was found to be a predictor of needing additional therapy which corroborated findings from a study among RTRs in Canada.[8] This result may be explained by the distribution of age in this cohort. Nearly half of the patients were over 50 years old and were not receiving the vaccinations stated above.

Dyslipidemia was found to be significantly associated with the need for additional therapy on univariate analysis. Studies have found that the prevalence of dyslipidemia is high among RTRs.[24,25] The predisposing factors of dyslipidemia include: immunosuppressive agents, advanced age, coexisting diabetes mellitus and use of beta blockers in management of hypertension.[25] Several studies, show that dyslipidemia is associated with cardiovascular complications among RTRs.[24–26] Guidelines recommend lifestyle modifications and use of statins in the management of dyslipidemia.[6]

The prevalence of non-adherence among RTRs was low and was consistent with findings from other studies. [27–29] The causes of non-adherence in this study were unintentional and included unaffordability of the drug product, forgetfulness and unavailability of the medicine. The high cost of immunosuppressive medication was the main cause of nonadherence. This would perhaps be attributed to RTRs refilling their prescriptions out-of-pocket. A previous study showed that more than 10% of RTRs were nonadherent because of difficulty associated with the ability to directly pay for the medications.[30] Forgetfulness was cited as a cause of nonadherence which is supported by several studies.[28,31–33] The plausible explanations for forgetfulness were disruptions in normal routines, travelling and inadvertent forgetfulness. Unavailability of medicines was also reported as a cause of non-adherence in a study conducted in Iran.[34]

The number of comorbidities, number of medications and BMI were found to be independent predictors of non-adherence among the participants. The strongest predictor of non-adherence was multiple comorbidities as supported by previous studies.[27,32] This finding may be explained by the fact that multiple comorbidities necessitate polypharmacy which is likely to burden the patients leading to non-adherence.[4,10,15]

In univariate analysis employment status was associated with non-adherence among participants. Unemployed patients are unlikely to afford medication because insurance does not cover post-transplant medicines. Studies have shown that employment is a predictor for non-adherence among RTRs.[28,32] However, this finding was not statistically significant in multivariate analysis.

BMI was found to be a predictor of non-adherence in multivariable logistic regression analysis. Underweight patients were more likely to be non-adherent than patients with normal weight. Perhaps underweight patients were unable to tolerate the medicines. This is a novel finding of the study requiring further study.

Most participants experienced undesirable effects as a result of medication use. This prevalence was high compared to a previous study.[11]The possible explanation for the difference is that the previous study only documented ADRs which were severe and requiring clinical interventions while the present study documented all ADRs. The most frequently implicated drug classes in this study were immunosuppressive and antihypertensive agents. This finding is consistent with other similar studies.[11,34]This result may be explained by the fact that immunosuppressive agents have a narrow therapeutic index and propensity for drug-drug interactions. There was no significant association between the socio-demographic, clinical characteristics and adverse drug reaction.

In this study, self-reported adherence score was used, which may have inadvertently resulted in high scores where participants overstated their adherence. Additionally, being a cross-sectional study, causation between the

predictors and DTPs could not ascertained. However, the present study has identified socio-demographic and clinical characteristics of participants associated with DTPs which may provide insight for developing strategies to prevent DTPs among RTRs.

CONCLUSION

Adverse drug reactions, additional drug therapy needed and non-adherence were the most common DTPs identified among RTRs. Advanced age >60 years was a major predictor of additional drug therapy neeeded while the number of medications, comorbidities and BMI were found to be independent predictors of non-adherence among RTRs.

The findings of this study indicate there is a need for a public health vaccination program especially among older RTRs for vaccine-preventable diseases. In additionally, targets to mitigate DTPs should be intensified among the elderly lean individuals with multiple medications due to comorbidities. Further longitudinal research is need to ascertain the causation of DTPs with the factors identified.

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