

## **Polypharmacy and predictors of high level polypharmacy in patients with diabetic nephropathy in a tertiary care hospital**

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**Received:** 08 April 2019

**Accepted:** 07 May 2019

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### **ABSTRACT**

**Background:** Diabetic Nephropathy (DN) is the leading cause of end-stage renal disease. Polypharmacy is common in DN as pharmacotherapy is complex with multimorbidity. The objectives of the study are to assess the prevalence and patterns of polypharmacy and to determine the predictors of high-level polypharmacy among patients with diabetic nephropathy in a tertiary care hospital.

**Methods:** A prospective observational study was conducted among adult patients with DN visiting nephrology outpatient department (March 2015 to August 2016). Data on demography, disease characteristics, and treatments were collected. Baseline data were summarized using descriptive statistics. Categorical variables and predictors of polypharmacy were analysed using Chi-square tests and multivariate logistic regression respectively.

**Results:** Mean age of patients was 58.14±10.44 years with male preponderance (72.7%). A majority of patients had comorbidities (76%). Hypertension was the most common co-morbidity (98.7%). Majority (64%) were in DN stage 4-5 and 58% of patients were undergoing hemodialysis. Mean number of drugs prescribed was 9.25±2.5. Anti-hypertensives (95.3%) were the major drug class prescribed. Polypharmacy (>5 drugs) was noticed in 95.3% patients and high-level polypharmacy (>10 drugs) in 46.7%. Presence of ≥3 comorbidities is a significant predictor of high-level polypharmacy (OR-1.414; 95% CI (1.008, 1.982), p=0.045).

**Conclusions:** Polypharmacy was noticed in a majority of patients with high level polypharmacy in more than one third of patients with DN. Presence of ≥3 comorbidities were found to be significant predictor of high-level polypharmacy.

**Keywords:** Diabetic nephropathy, India, Multimorbidity, Polypharmacy, Predictors

### **INTRODUCTION**

Diabetic nephropathy (DN) is one of the common microvascular complications of diabetes mellitus. It is a leading cause of end-stage renal disease and a contributor to significant morbidity and mortality in patients with diabetes.<sup>1</sup> The mortality burden in DN is 23.5% as compared to non-diabetics (6.1%, P=0.072) in India.<sup>2</sup> Slowing the rate of disease progression in the early stages of DN is a major goal, together with monitoring and correcting its complications and co morbidities, and

treating the underlying disease. Pharmacotherapy for DN is complex as it is usually associated with multimorbidity. Multimorbidity can present several challenges in patient care particularly with higher numbers of coexisting conditions and related polypharmacy.<sup>3</sup> Polypharmacy is defined as the concurrent prescribing of >5 drugs.<sup>4</sup> Polypharmacy is common in DN as there are multiple comorbidities and it can lead to problems like non adherence, adverse drug reactions, drug interactions and increased cost of therapy.<sup>5</sup>

The objectives of this study were to assess the prevalence and patterns of polypharmacy and its predictors. No studies were identified from India using the MeSH terms (DN, Polypharmacy, drug, India) in Pubmed from 2004-2014 with the best of our knowledge. This study was expected to provide a comprehensive review on polypharmacy in DN, to recommend suggestions in comparison with evidence-based therapies.

## METHODS

Authors conducted a prospective, observational study at an Indian tertiary care hospital with a large dialysis facility over 18 months. Recruitment was done from March 2015 to August 2016. Ethics approval for the study is obtained from Institutional Ethics Review Board (IERB). The IEC reference number for the study is 115/2015. The study was explained in the language understood by the patient and informed consent was obtained. Authors included patients diagnosed with diabetic nephropathy all stages, aged  $\geq 18$  years irrespective of whether they were on dialysis. Authors excluded patients undergoing renal transplant and peritoneal dialysis. Authors collected demographic, laboratory and treatment data. Demographic data includes age, gender and socio-economic status (education, income, occupation). Medical history includes family history, disease characteristics, stage of disease CKD and DN, duration of the disease, comorbidities, presence of dialysis and frequency of dialysis.

According to literature, mean no. of drugs per patient in DN is  $7 \pm 2.6$ . With relative precision of 5% and CI = 95%, assuming 20% drop outs, sample size is estimated as 150 patients to assess the prevalence and patterns of polypharmacy in DN.

Baseline data were summarized as mean  $\pm$  SD. Descriptive statistics were used to analyze data on demography, disease characteristics, key laboratory investigations. Data on the prevalence of polypharmacy, were analysed using descriptive statistics. Two groups were formed based on polypharmacy (with polypharmacy and without polypharmacy) and the categorical variables like gender, age category, socio-economic status, stage of DN and CKD, presence or absence of dialysis were compared between the groups using Chi-squared tests. To assess the predictors of polypharmacy in patients with DN, binary logistic regression followed by multivariate logistic regression analysis was performed. High level polypharmacy (concurrent prescription of ten or more drugs) was taken as the dependent variable and independent variables used were the patient characteristics (age, sex, socio-economic status) and disease characteristics (stages of DN and CKD, comorbidities and presence of dialysis). A p value  $< 0.05$  will be considered significant for all tests. Statistical analysis was performed using commercially available software, Statistical Package for the Social Sciences version 16.0 software (SPSS Inc, Chicago, IL, USA).

## RESULTS

Among the 150 DN patients recruited, 109 (72.7 %) were males. The mean age was  $58.14 \pm 10.44$  years. Majority of the patients had a family history of diabetes, 93 (62.0%), followed by hypertension 60 (40.0%) and chronic kidney disease 16 (10.7%) respectively (Table 1).

Authors classified the patients according to stages of DN and CKD. Hypertension was the most common comorbidity seen in 148 (98.7%) DN patients, followed by diabetic retinopathy, present in 91 (60.7) patients.

**Table 1: Baseline characteristics.**

Baseline characteristics	No. of patients (N=150)	
Mean age in years $\pm$ SD	58.14 $\pm$ 10.44	
Gender, n (%)	Male	109 (72.7)
	Female	41 (27.3)
Age category, n (%)	<60 years	76 (50.7)
	$\geq 60$ years	74 (49.3)
Place of residence, n (%)	Rural	47 (31.3)
	Urban	103 (68.7)
Habits	Smoking	32 (21.3)
	Alcohol	32 (21.3)
	Tobacco chewing	04 (02.7)
Socio-economic status, n (%)	Rich	15 (10.0)
	Upper middle	45 (30.0)
	Lower middle	62 (41.3)
	Upper lower	24 (16.0)
Family History, n (%)	Lower (poor)	04 (02.7)
	Diabetes	93 (62.0)
	Hypertension	60 (40.0)
	Chronic kidney disease	16 (10.7)

Other cardiovascular co-morbidities like coronary artery disease and stroke were seen in 36 (24.0 %) and 06 (4.0%) patients respectively. Hypothyroidism was reported in 32 (21.5%) patients and liver disease in 15 (10.0%) patients.

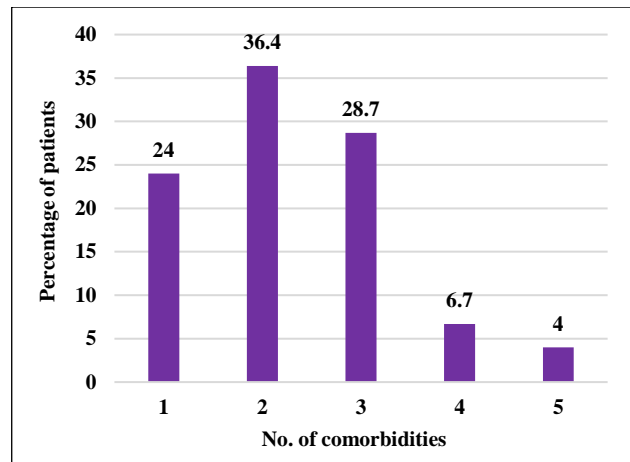
There were other comorbidities like diabetic foot in 16 (10.7%) patients, seizure disorder in 3 (02.0%), bronchial asthma in 2 (01.3%) and psychiatric illness in 1 (0.7%) patient. Details are presented in Table 2.

Among the 150 patients with DN, 87 patients (58.0%) were undergoing hemodialysis as the renal replacement therapy. 50 patients (57.5%) were undergoing dialysis twice a week, 35 patients (40.2) three times a week, 2 patients (02.3%) once a week (Table 2).

**Table 2: Disease characteristics of DN patients at baseline.**

Disease characteristics		n (%), N=150	
Stages of CKD, n (%)	Stage I	17 (11.3)	
	Stage II	09 (06.0)	
	Stage III	23 (15.3)	
	Stage IV	13 (08.7)	
	Stage V	88 (58.7)	
Stages of DN, n (%)	Stage I	16 (10.7)	
	Stage II	11 (07.3)	
	Stage III	27 (18.0)	
	Stage IV	11 (07.3)	
	Stage V	85 (56.7)	
<b>Comorbidities n (%)</b>			
Hypertension		148 (98.7)	
Diabetic retinopathy		91 (60.7)	
Coronary Artery Disease		36 (24.0)	
Thyroid hypothyroidism		32 (21.5)	
Diabetic foot		16 (10.7)	
Liver disease		15 (10.0)	
Seizure		03 (02.0)	
Stroke		06 (04.0)	
Dyslipidemia		06 (04.0)	
Bronchial asthma		02 (01.3)	
Psychiatric illness		01 (00.7)	
Dialysis history, n (%)	No. of patients underwent dialysis		87 (58.0)
	Haemo-dialysis frequency	1 time/week	02 (02.3)
		2 times/week	50 (57.5)
		3 times/week	35 (40.2)

There are 24% of the patients with single comorbidity, 36.4% of the patients had 2 comorbidities, 28.7% of patients had 3 comorbidities, 6.7% had four comorbidities and 4% of the patients had 5 comorbidities (Figure 1).



**Figure 1: Distribution of comorbidities (multimorbidity) among DN patients.**

Mean number of drugs that the patients received in this study was 9.25±2.54. Anti-hypertensives (95.3%) were the major drug class prescribed.

Polypharmacy (patients who receive ≥5 drugs) was present in 143 patients (95.3%) high level polypharmacy (≥10 drugs) was noticed in 70 patients (46.70%) and low-level polypharmacy (≥5 drugs, but <10 drugs) in 73 patients (48.70%) (Table 3).

**Table 3: Pattern of polypharmacy in DN patients.**

Parameter	No. of patients (N = 150)	%	
Mean no. of drugs (SD)	9.25 (2.544)		
Polypharmacy	143	95.30	
Level of polypharmacy	Low	73	48.70
	High	70	46.70

Chi squared test was done to compare the characteristics of patients with polypharmacy and no polypharmacy. There is significant increase in the occurrence of polypharmacy with higher stages of DN (p =0.014) (Table 4). Bivariate analysis identified DN stages 4-5 (p=0.026), CKD stages 4-5 (p=0.005), presence of dialysis (p=0.024) as significant predictors of high-level polypharmacy.

On multivariate logistic regression analysis, presence of ≥3 comorbidities (OR=1.414, p=0.045) was found to be a significant predictor of high-level polypharmacy in patients with DN (Table 5).

**DISCUSSION**

To the best of our knowledge, this study is the first follow up comprehensive study in South India which evaluated the patterns and determinants of polypharmacy in patients with DN. The mean age of the patients in this study was 58.14 (±10.44) years with 72.7% males. This was comparable to the mean age of patients with overt nephropathy in CURES

study conducted in Chennai where the mean age was 57±9 yrs and a majority of patients were males (52%).<sup>7</sup>

**Table 4: Comparison of characteristics of patients with polypharmacy and no polypharmacy.**

Parameters		Polypharmacy	No polypharmacy	P value
Age category	≥60 years	70	6	0.495
	<60 years	73	1	
Gender	Male	103	6	0.705
	Female	38	3	
Dialysis	Present	83	3	0.127
	Absent	57	6	
Socioeconomic status	Upper	13	2	0.453
	Upper middle	44	1	
	Lower middle	58	4	
	Upper middle	22	2	
	Lower	04	0	
Stages of CKD	Stage I	15	2	0.130
	Stage II	08	1	
	Stage III	22	4	
	Stage IV	11	2	
	Stage V	85	0	
Stage of DN	Stage I	14	2	0.014*
	Stage II	10	1	
	Stage III	26	1	
	Stage IV	08	3	
	Stage V	83	2	
Comorbidities	<3	84	8	0.154
	≥3	57	1	

\*Compared using Chi-Square test, for cells with the count <5 Fisher's exact test was used. p ≤0.05 is considered statistically significant.

**Table 5: Predictors of high-level polypharmacy in patients with DN.**

Characteristics		Bivariate analysis			Multivariate analysis		
		OR	95% CI	P value	OR	95% CI	P value
Age category	<60 years	Ref			0.790	0.383-1.630	0.523
	≥60 years	1.150	0.596-2.216	0.139			
Gender	Female	Ref			-	-	-
	Male	1.167	0.558-2.439	0.682			
SES category	Lower	Ref			-	-	-
	Upper	1.354	0.693-2.645	0.375			
No. of comorbidities	< 3	Ref			1.414	1.008-1.982	0.045*
	≥ 3	1.939	0.981-3.832	0.057			
Stage of DN	Stage 1-3	Ref			0.333	0.084-1.324	0.119
	Stage 4-5	2.214	1.100-4.459	0.026			
CKD stage	Stage 1-3	Ref			3.652	0.956-13.943	0.058
	Stage 4-5	2.862	1.373-5.966	0.005			
Dialysis	Absence	Ref			0.677	0.205-2.234	0.522
	Presence	2.196	1.109-4.348	0.024			

\*Binary logistic regression followed by multivariate logistic regression is done and p < 0.05 is considered statistically significant.

In this study, 11.3%, 0.6%, 15.3%, 8.7% and 58.7% patients were in CKD stage 1, 2, 3, 4 and 5 respectively. In the Indian CKD registry, the proportion of DN patients in

CKD stage 1, 2, 3, 4 and 5 are 1.7%, 4.2%, 20.2%, 27.2% and 47.3% respectively. The proportion of CKD stage 5 patients in our study was higher than other stages which is

comparable to the above registry. The patients in this study on an average underwent 8 dialysis sessions per month which was comparable with the study by Satyavani K et al, done in a South Indian state.<sup>8</sup>

KDOQI (Kidney disease outcomes quality initiative) clinical practice guideline recommends 3-4 dialysis sessions per patient per week.<sup>9</sup> This was not affordable to many patients as around 90% belonged to lower to middle class socioeconomic strata in this study. Among the patients who were undergoing dialysis in this study, 55.7% belong to lower socioeconomic status. Satyavani K et al, showed that among patients on dialysis, 80% had monthly income below INR 20,000 and 47% below INR 10,000. The cost of diabetes treatment is an out-of-pocket expenditure for many patients in developing countries such as India. In the absence of insurance policies for diseases such as diabetes and meager financial support from the public health-care sector, patients spend from their personal savings and face a huge financial crisis.

Arterial hypertension is a main risk factor for the development of DN. In this study, hypertension was the most common comorbidity present in 148 patients (98.7%) as similar to CURES study that showed 86.7% of patients had hypertension with overt nephropathy.<sup>7</sup>

In this study, about 58% of the patients were on hemodialysis and 57.5% of them were undergoing dialysis 2 times per week while 40.2% underwent dialysis 3 times per week, according to the UK clinical guidelines on hemodialysis.<sup>10</sup>

The mean no. of drugs per day in our study was  $9.25 \pm 2.54$ . This is comparable to the study on CKD patients in Brazil where the average no. of drugs per day was  $8.5 \pm 4.3$ .<sup>11</sup> In this study, anti-hypertensives were the most commonly prescribed (95.3%) drugs.

Since diabetic nephropathy is usually associated many comorbidities like hypertension, dyslipidemia, CAD, heart failure etc, the treatment of this condition is complex involving multiple medications. So, polypharmacy is common in this condition. Multimorbidity in the general population is associated with polypharmacy.<sup>12</sup> In this study, 95.3% of patients had polypharmacy, out of which 46.7% had high level polypharmacy (prescribed  $\geq 10$  drugs). The prevalence of polypharmacy was 56.72% in patients with CKD in a study conducted among 1300 patients aged above 60 years in US.<sup>13</sup> In this study, authors got the number of comorbidities  $\geq 3$  as a significant predictor of high-level polypharmacy. The patients with DN have multiple comorbidities that predispose to multiple medications.<sup>14</sup>

Authors have conducted a comprehensive, prospective study that looked at demography, clinical features and pattern of polypharmacy in patients with DN. It was carried out on an estimated sample size of 150 DN patients. Being a tertiary care setting, authors had representation from

different sections of the society. Multimorbidity was found to be a significant predictor of polypharmacy.

Present study provided reliable and relevant information on multimorbidity and polypharmacy among Indian patients with DN and this could be used as a support for better patient management and also for future research.

*Funding: No funding sources*

*Conflict of interest: None declared*

*Ethical approval: The study was approved by the Institutional Ethics Review Board (No. 115/2015)*

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**Cite this article as:** Jose JV, Devi P, Satish R. Polypharmacy and predictors of high level polypharmacy in patients with diabetic nephropathy in a tertiary care hospital. *Int J Basic Clin Pharmacol* 2019;8:1371-6.