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Management practices, adherence and non-adherence among patients with chronic kidney disease at tertiary care hospital

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Abstract
Chronic kidney disease (CKD) is an increasingly recognized major public health problem globally and in Nepal. It has a high prevalence in the population and is associated with high morbidity, mortality and health care costs. Chronic kidney disease (CKD) has a complicated interrelationship with other diseases. Management of CKD patients therapeutically is complicated due to co-morbidities and various complications of CKD, non-adherence to treatment is an overgrowing problem for patients with CKD. Hence, the present study is carried out to assess the management practice, medication adherence and non-adherence at tertiary care hospital.

Keywords: management practice, chronic kidney disease, medication adherence and non-adherence

1. Introduction

Chronic kidney disease (CKD) is defined as abnormal kidney function existing greater than 3 month [1] or the estimated glomerular filtration rate (eGFR) below 60ml/min/1.73m^{2}with or without kidney damage [2]. It is a progressive, irreversible deterioration in kidney function in which the body's ability to sustain metabolic, fluid and electrolyte balance fails [3]. If the damage is very bad, kidneys may stop working, this is called kidney failure, or end-stage renal disease (ESRD), if kidneys fail, we need dialysis or a kidney transplant in order to live [3]. The prevalence of CKD in the population is a considerable social and economic problem worldwide, and one that is increasing. It often goes undetected and undiagnosed until their kidney function is down to 25% of normal [4]. Globally, 10% of the population is affected by CKD, and millions die each year due to high economic cost treatment [1].

1.1 Markers of Kidney damage

Albunimuria, urinary sediments abnormality, electrolyte abnormality due to tubular disorder, abnormalities on histology, structural abnormalities detected by imaging, and history of kidney transplantation [3].

1.2 Stages of Chronic kidney disease

Estimated Glomerular filtration rate between 90-120ml/min/1.73m^2 is considered as normal. Chronic kidney disease is classified according to the eGFR, as stage 1(normal or high) eGFR> 90ml/min/1.73m^2,stage2 (mildlydecreased) eGFR60-89ml/min/1.73m^2,stage 3a(Mild to moderately decreased) eGFR45-59ml/min/1.73m^2, stage3b (Moderate to severely decreased)eGFR30-44ml/min/1.73m^2, stage 4(severely decreased) eGFR 15-29ml/min/1.73m^2, and stage 5 (ESRD/Kidney failure) eGFR< 15ml/min/1.73m^2 [2].

1.3 Causes of Chronic kidney disease

The causes of CKD vary globally, and the most common primary diseases causing CKD and ultimately end-stage renal disease (ESRD) are Diabetes mellitus type 2 (30% to 50%), Diabetes mellitus type 1(3.9%), Hypertension (27.2%), Primaryglomerulonephritis (8.2%), Chronic Tubule interstitial nephritis (3.6%), Hereditary or cystic diseases (3.1%), Secondary glomerulonephritis or vasculitis (2.1%),Plasma cell dyscrasias or neoplasm (2.1), Sickle Cell Nephropathy (SCN) which accounts for less than 1% of ESRD patients [5].

1.4 Co-morbidities

Co-morbidities are any distinct additional entity that has existed or may occur during the clinical course of a patient who has the index disease under study [6]. CKD has a complicated interrelationship with other diseases, most commonly diabetes mellitus, hypertension, glomerulonephritis and CVD like peripheral vascular disease, atherosclerosis, ischemic heart disease etc. [7].

1.5 Complications

It is an unfavorable result of a disease, health condition, or treatment. Complications generally involves in the worsening in severity of disease. Complications may lead to the development of new diseases resulting from a previously existing disease. CKD complications include anemia, osteodystrophy, cardiovascular risk, dyslipidemia, hyperkalemia, gout, hyperphosphatemia etc [8].

1.6 Medication adherence

Adherence to medication is defined as "the extent to which the patient's behavior matches agreed on recommendations from the prescriber'' [9]. CKD is a prolonged illness usually co-existing with diseases such as hypertension and diabetes, consequently they have to take a large pill burden on an average of around 8–10 tablets/day, so adherence is the major concern in the therapy of CKD, so adherence to medication is a key component of effective disease management in CKD [10].

1.7 Non-adherence

The condition when patient fail to comply the instruction given by pharmacist or health care professional [11]. So, non-

adherence or low medication adherence are the major indicating factor for sub-optimal health outcome, therapeutic failure, patient safety and health care cost [12].

1.8 Non-adherence and causes of non-adherence in CKD

Non-adherence to medications is quite common in chronic diseases, and may be seen in over 50% of the patients [13]. Studies have shown that non-adherence in CKD caused, uncontrolled hypertension, more frequent dialysis, increase in expense of medications and hospitalization [14]. Thus, non-adherence reduces the beneficial effects of drugs and can eventually lead to CKD progression and occurrence of end-stage renal disease [15]. The major predictors of the poor adherence include high cost of medications, forgetfulness, high pill burden, complex dosing schedule, poor knowledge of disease/treatment in physicians, adverse effects/side effects, psychosocial issues, and not feeling well without medications [16, 17].

1.9 Management practices in CKD

Lifestyle modifications (dietary management, weight management, physical activity) are the initial components of treatment and secondary prevention. Blockade of the renin angiotensin aldosterone system with either an angiotensin converting enzyme inhibitor (ACEI) or an angiotensin receptor blocker (ARB) is the cornerstone of treatment to prevent or decrease the rate of progression to end-stage renal disease. Blood pressure control reduces renal disease progression and cardiovascular morbidity/mortality. Optimally manage comorbid diabetes and address cardiovascular risk factors to decrease risk for cardiovascular disease, which is the leading cause of mortality for patients with CKD. Statin or statin/ezetimibe therapy is recommended in all CKD patients age ≥ 50 years to decrease the risk of cardiovascular or atherosclerotic events. Monitor for other common complications of CKD including: anemia, electrolyte abnormalities, abnormal fluid balance, mineral bone disease,and malnutrition, avoid nephrotoxic medications to prevent worsening renal function [18].

2. Materials and Methods

Study Design: Prospective, observational study, cross sectional study

Study Site: Department of nephrology of tertiary care at UCMS Teaching hospital

Sample Size: Minimum 85 patients

Study Duration: 9 months from April 2019 to December 2019.

Study criteria

Inclusion criteria

- All CKD patients and on medications for more than 3 months irrespective of the stages of CKD.
- 18 years and above patients.
- Patients who are willing to participate and give the consent form.

Exclusion criteria

Patients refused to participate in the study.

Patients with cognitive impairment.

Socio-demographic data

The data collected in this section included sex, age, marital status, occupation, education status, yearly family income and duration of the disease.

Morisky medication adherence scale-8 (MMAS-8)

In this study, we used the 8-items MMAS, which includes 7 questions with yes/no response option and 1 item with a 5-point likert scale response option. The MMAS-8 results in a score ranging from 0-8, and developers suggested three levels of medication adherence on the basis of this score: poor, medium and high with >2,1or 2, and 0 respectively [49].

Source of data

Inpatients: Patients case records file, and medication chart/cardex.

Outpatients: Prescriptions on OPD book/card.

Sample size

The sample size is calculated using single population proportion formula as follows [28].

$$n = \frac{Z^2 P(1-P)}{d^2}$$

Where;

n =desired sample size.

Z = standard normal distribution usually set as 1.96 (which corresponds to 95% confidence)

P =expected prevalence 10.6% (that can be obtained from same studies or a pilot study conducted by the researchers). Negative prevalence = 1 −0.106 = 0.894,

d = degree of accuracy desired (marginal error is 0.066); then the sample size is.

$$n = \frac{1.96^2 \times 0.106(1-0.106)}{0.066^2} = 83.57 = \approx 85$$

Study procedure

First of all, the study was approved by institution ethical committee. Then consent form was obtained from patients who were willing to participate in the study. The data was taken randomly from the sample of 85 patients from the in-patients, out-patients department and hemodialysis/nephrology unit. The required details/data were collected using structured questionnaires to extract information from the patients and disease related data abstraction format were also used to extract information from medical records file, medication cardex, patients OPD card and by direct interviews of the same patients at the same time.

Statistical analysis

1. All the data was entered into SPSS version-20 statistical software for analysis.
2. Descriptive statistics were used to describe patients baseline characteristics.
3. The chi-square test was used to determine P-value.
4. P-value was used to determine the statistical significance i.e association between medication adherence and independent variables (socio-demographic of patients).
5. P-value ≤ 0.05 (5%) was considered as statistically significant.

3. Results

3.1 Socio-demographic characteristics

3.1.1 Sex distribution

Figure (I) indicates male comprised majority of the sex category i.e. 55(64.7%).

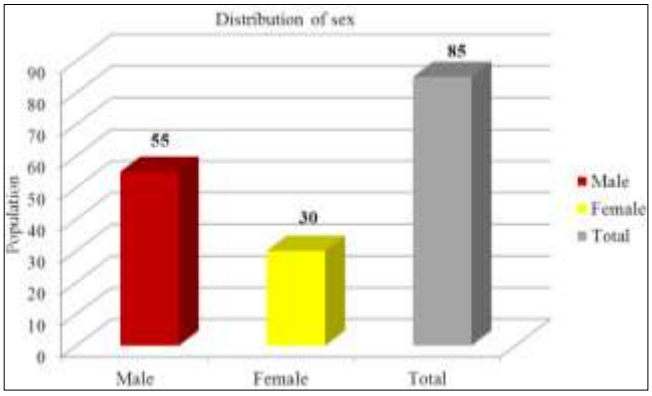

Fig 1: Sex distribution of population

3.1.2 Age distribution

From figure (II), majority of the population were in the age group of less than 65 years. Which accounted for 84.7%.

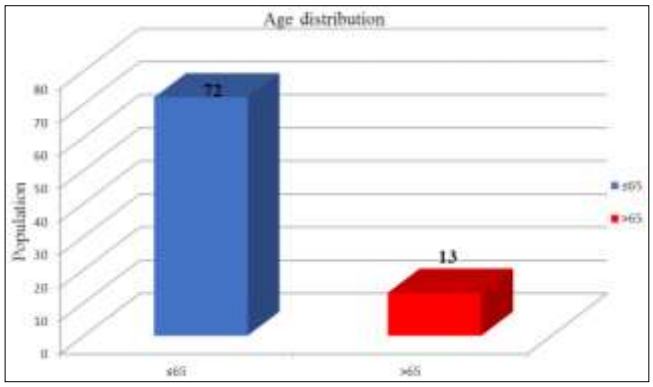

Fig 2: Age distribution of population

3.1.3 Marital status

The marital status was as shown in fig (III) and the majority of the population were married which comprised 85.9% of the marital status category.

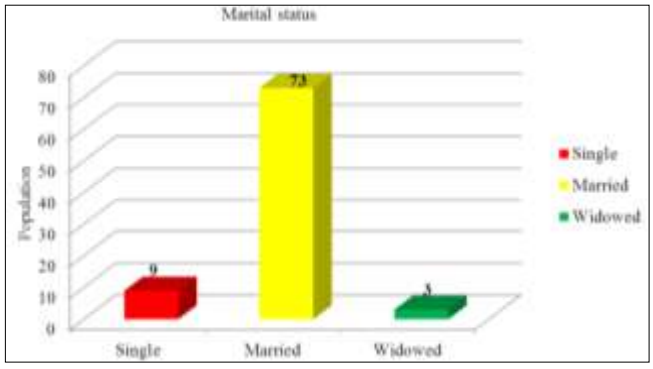

Fig 3: Marital status of population

3.1.4. Occupation

From fig (IV), house wife comprised majority of the population, which accounted for 25.9%.

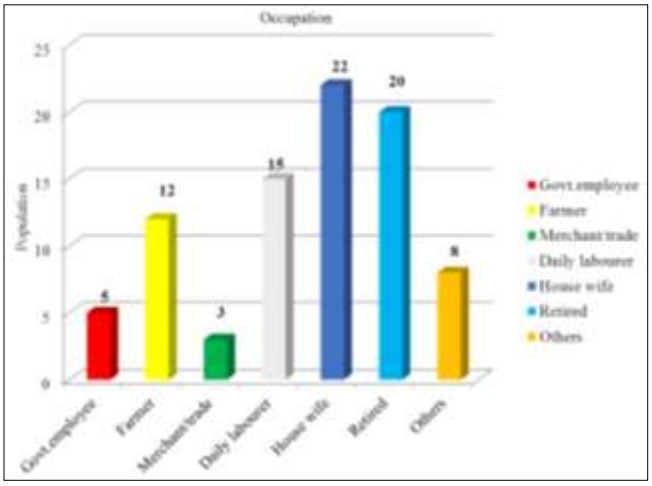

Fig 4: Occupation of population

3.1.5. Education status

From figure, the majority of the population/patients were, cannot read and write and comprised 56.5% of the patients.

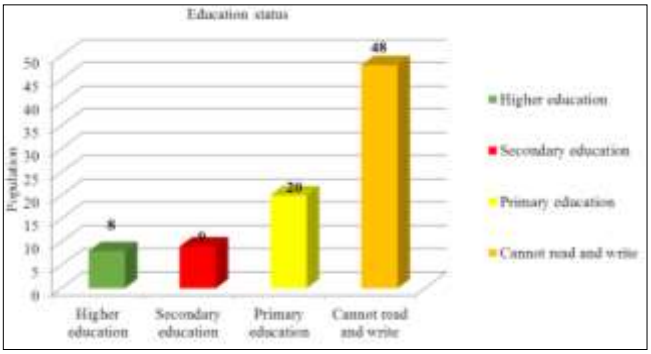

Fig 5: Education status of population

3.1.6. Yearly family income

From the figure, average family income (1-5lakh) per year was in the majority of population, which accounted for 61.2%.

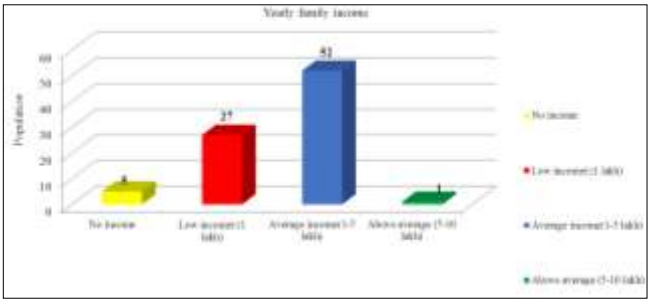

Fig 6: Yearly family income of population

3.1.7. Duration of CKD in years

From figure, majority of participants having 1-5 years of duration of CKD had comprised 48.2%.

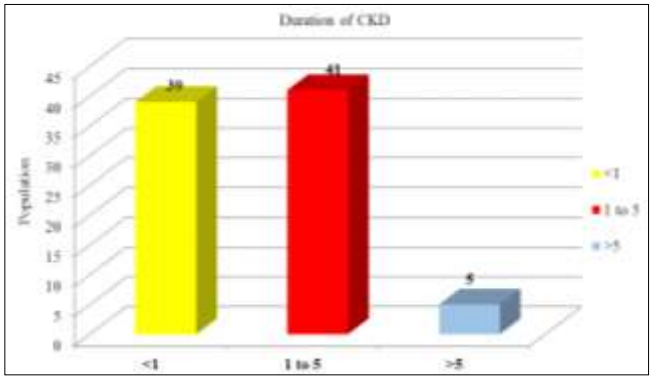

Fig 7: Duration of CKD of population

3.1.8. Level of medication adherence

Assessment of patient's response to the 8-item Morisky Medication Adherence Scale showed that 28(32.9%), 20(23.5%) and 37(43.5%) patients exhibited high, medium and poor adherence to the prescribed regimens, respectively.

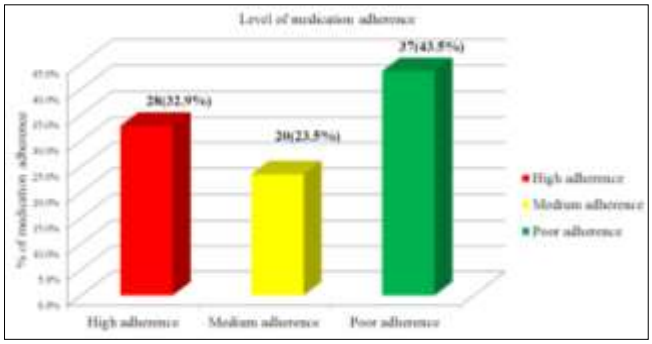

Fig 8: Level of medication adherence

3.1.10. Association of socio-demographic characteristics with medication adherence

Table 1: Chi-square test analysis for association between socio-demographic and adherence

Variables	Level of Medication Adherence			Chi-square test	P-value
	Poor adherence	Medium adherence	High adherence		
Sex					
Male	24(64.9%)	19(45%)	22(78.6%)	5.75	0.056
Female	13(35.1%)	11(55%)	6(21.4%)		
Age in years					
≤65	26(70.3%)	19(95%)	28(100%)**	13.41	0.001*
>65	11(29.7%)**	1(5%)	0		
Occupation					
Farmer	8(21.6%)	2(10%)	2(7.1%)	35.26	0.000*
govt.empoyee	1(2.7%)	1(5%)	3(10.7%)		
Merchant/trade	0	1(5%)	2(7.1%)		
Daiy labourer	5(13.5%)	4(20%)	6(21.4%)		
Housewife	8(21.6%)	8(40%)	6(21.4%)		
Retired	15(40.5%)**	4(20%)	1(3.6%)		
Others***	0	0	8(28.6%)**		
Education status					
can't read &write	28(75.7%)**	12(60%)	8(28.6%)	21.14	0.002*
Primary	6(16.2%)	6(30%)	8(28.6%)**		
Secondary	3(8.1%)	1(5%)	5(17%)		
Higher Edu.	0	1(5%)	7(25%)		
Income (in years)					
no income	2(5.4%)	2(10%)	1(3.6%)	6.27	0.393
low(≤ 1akh)	12(32.4%)	9(45%)	6(21.4%)		
Average(1-5lakh)	23(62.2%)	9(45%)	20(71.4%)		
above average	0	0	1(3.6%)		

*Statistically significant at P≤0.05, ***driver, teachers and students

Variables such as sex, age, occupation education status and yearly family income were included in the chi-square analysis. Based on the results from the analysis, only age (P=0.001), occupation (P=0.000), and education status (P=0.002) of patients had significant association with CKD medication adherence. Age group of ≤ 65 were more adhered to medications than age above 65. Patients having other occupations like teacher, driver and students were more adhere to medications than retired patients and other occupations. Retired patients were less adhered to medications. Patients who were educated had significant association with their medication adherence and adhered more than the patients who cannot read/write or uneducated.

3.2 Management practices for co-morbidities and complications

It included the pharmacological treatment for management of CKD co-morbidities and complications.

3.2.1 Profile of prescribed medication

Table 2: List of prescribed medication

S. No	Variables	Frequency	Percentages (%)
1	Angiotensin converting enzyme inhibitors	0	0%
2	Calcium channel blockers		
	Amlodipine	68	80%
	Nifedipine	4	5%
3	Diuretics		
	Furosemide	66	78%
	Torsemide	18	21%
4	Beta-blockers		
	Atenolol	1	1%
	Metoprolol	10	12%
	Carvediol	8	9%
5	Angiotensin receptor blockers		
	Losartan	6	7%
6	Alpha-blockers		
	Prazosin	28	31%
7	Anti-diabetic		
	Insulin	26	31%
8	ASA(aspirin)	1	1%
9	Antibiotics	25	29%
10	Iron	55	65%
11	Erythropoitin	12	14%
12	Calcium formulation/suppliments*	46	54%
13	Statins/Atorvastatin	6	7%
14	Febuxostat	12	14%
15	Others*	36	42%

Sodiumvalporate, glicazide, linagliptin, metolazone, clopodogrel, levothyroxine, sodium, clonidine, vit.B6, propranolol, alfuzosin, salmetrol, theophylline, tamsulosin, sodium bicarbonate, sevelamerHCL, vit.D, labetalol, lanthanumcarbonate.antibiotics; pyrazinamide, isoniazide, rifampicin, cefixime, ethambutol, cotrimazole, levofloxaxin, piperacillin & tazobactum, linezolid. Calcium supplements: calium+vit. D & calcium formulations.

From the table, a calcium channel blocker, amlodipine is prescribed in the majority of patients, which accounted for 68(80%). Diuretics, furosemide is also prescribed in the majority of patients, which accounted for 66(78%).

3.2.2 Management practice for co-morbidities

Table 3: Types of regimens used in the management of CKD comorbidities

Comorbidities	Frequency	Percentages (%)
1. Hypertension		
ACEI based regimens	0	0%
Non-ACEI based regimens	72	85%
2. Diabetes Mellitus + Hypertension		
Insulin + ACEI based regimens	0	0%
ACEI based regimens	0	0%
Metformin + ACEI based regimens	0	0%
Metformin + Non - ACEI based regimens	0	0%
Insulin + Non - ACEI based regimens	21	25%
others*	2	2%
3. Diabetes mellitus		
Insulin	5	5%
Metformin	0	0%
Glibenclamide	0	0%
Insulin + Glibenclamide	0	0%
others**	0	0%
4. Dyslipidemia		
Statins	6	7%
5. CVD		
Statins	1	1%
Anti – hypertensives + Diuretics	1	1%
Others***	2	2%
6.Others****	5	6%

*Linagliptin, glicazidetorsemide and amlodipine, **No other drugs were used for DM, ***Clopidogrel and aspirin, ****levothyroxinsodium, salmetrol and theophylline

From the table, it was identified that the hypertension was managed by 85% of non-ACEI, there were no priscription of ACEI based regimens for hypertension. Non-ACEIs drugs on my study were the drugs rest of ACEI. Participants having both diabetes mellitus and hypertension, were managed by insulin+non-ACEI based regimens in majority, that accounted for 25%. Diabetes mellitus alone was managed by insulin only, which accounted for 5%.Dyslipidemia was managed by 7% of statins. Cardiovascular diseases was managed by the use of statins, clopidogrel, aspirin and antihypertensive diuretics in somewhat equal proportion. Other comorbidities like COPD and hypothyroidism were managed by the use of salmetrol, theophylline, and levofloxacin sodium respectively in 6%.

4. Discussion

In the present study, different medications were used in the management of co-morbidities and complications of CKD. Amlodipine and furosemide were prescribed in 80% and 78% of CKD patients respectively. Anti-hypertensive therapy remains the most effective strategy for slowing the progression of Chronic kidney diseases [3]. Some studies, and various clinical guidelines stated the use of ACEIs and ARBs as the mainstays of hypertension treatment in CKD [29]. But based on co-morbidities status, non-ACEI based combination were the most commonly used treatment regimens in the management of hypertension alone [30], which is in agreement with my study where highly non-ACEIs regimens were used. There were no used of ACEIs based regimens in my study this might be because of the absence of concurrent albuminuria (albumin excretion > 300 mg/d), high potential risk of hyperkalemia, and moreover it is not effective in the high blood pressure control. Calcium channel blockers commonly amlodipine is used in combination as blood pressure control with or without diabetes mellitus in non-proteinuric patients [31]. Other non-ACEIs drugs were used as combination therapy mostly alpha-blockers like prazosin since they are less effective, which is in aggrement with the clinical guidelines done by Dan Pugh and Peter J. Gallacher [31]. Similarly, diuretics are frequently used as part of combination drug therapy in CKD and offer antihypertensive and cardio protective effects, also helps to decrease the fluid or volume overload [31].

Regarding the management of diabetes and hypertension, the present study revealed that combination of insulin and non-ACEIs based combination were the most commonly used treatment regimen which is in accordance with the study of Vikram Patney, Adam Whaley-Connell, and George Bakris [32]. But my study is in contrast with study done by Belayneh kefale, Yewondwossen *et al*. [30], where insulin and ACEIs combination were used commonly for the treatment of diabetes with hypertension,this contrast might be due to the high prevalenced of non-proteinuric patients.

The most widely used treatment agent in the management of diabetes co-morbidities alone was insulin,which accounted for 31%.The result of this study is comparable with the similar studies by Albers *et al* [33] and Dasari *et al* [34] which concluded the safely managed diabetic kidney disease.The common use of insulin is due to its safety upto the eGFR< 10ml/min. This study didn't found the prescription of metformin, because it is contraindicated in DKD because it undergoes renal excretion and its most serious adverse effect is the risk of lactic acidosis, and gliclazide have a lower risk of severe hypoglycemia than glibenclamide and can be prescribed in renal impairment if appropriate attention is paid to the dose but use should be avoided if the GFR falls to <40 mL/min [35].

Statins drug was higly prescribed for the management of dyslipidemia and CVD in the study,this might be due to the role in preventing progression of kidney disease and reducing albuminuria [35].

About the management of CKD complications, this study found the use of iron therapy with iron in combination with folic acid predominantly prescribed in the treatment of anemia, also the erythropoietin was prescribed for anemia treatment, which is in agreement with [36] as an effective drugs for anemia CKD complications. But erythropoietin was prescribed less inspite of iron therapy, although it is highy effective drug for anemia because of the economic constraints and its less availability in western region of Nepal. Cacium formulations/suppliments were prescribed more in the treatment of oesteodystrophy, which is in accordance with the guidelines [37]. Hyperkalemia was treated by the prescription of calcium gluconate and loop diuretics in my study, some study suggest the use of insulin with glucose in hyperkalemic emergency [38], along with the drugs in the present study. Most of the fluid buildup was managed by the prescription of furosemide and other loop diuretics, because loop diuretics have an estimated glomerular filtration rate (eGFR)<30mL/min/1.73m2 because other diuretics, including thiazide, are less effective in advanced CKD [39]. Which is in aggrement with the study. Hyperphosphatemia was treated by the prescription of sevelamer HCL, calcium acetate and lanthanum carbonate in the study, calcium acetate is more efficacious and cost effective than sevelamer and lanthanum in the treatment of hyperphoshatemia [40].

In the study adherence to the medication was observed in 32.9% of the patients. This finding is similar with the literature study conducted in National kidney center [26]. The study finding is also similar with the previous studies conducted in India [41] though the sample size is different. It is different from other studies conducted in US [42] and Saudi Arabia [43]. The variation might be due the differences in the methodologies between the studies.Just for example, direct adherence assessing methods, includes drug concentration assays, use of pill markers and direct observation of pill taking, while the indirect methods includes patient self-reports (structured interview), compliance rating by nurses, prescription refills [44]. In the light of poor management of CKD co-morbidities and complications, and failure of therapeutic regimen, health care providers should measure CKD patients' treatment adherence. Long term efforts are needed to elevate the medication adherence of these patients so that they could realize the full benefits of prescribed medications. When accurate information on the importance of medication adherence is provided, patients are encouraged towards self-care and adherence to drug therapy. Healthcare providers must be more cautious towards recognizing adherence problems in order to provide best interventions. On-adherence to prescribed regimens is life-threatening and more expensive in kidney patients [45]. Various studies reported that medication non-adherence had been associated with increased risk of co-morbidities, hospitalization and healthcare expenditure burden [46].

In the study, chi-square analysis revealed that age, occupations, and education status were found to be to be

significantly associated with CKD medication adherence. The age group below the elderly group were more adhered to medication than elderly group because they were more conscious about their remaining lives and they had less liability of medication forgetfulness. The older age group might had the memory degeneration, their physical and mental health were somewhat degraded to adhered the medication. More over occupation had significant association with CKD medication adherence. The patients who were students, teachers and driver were more likely to adhered compared to those who were retired from their job, which is in agreement with same study conducted Belayneh Kefale *et al* [47]. The retired patients might be less aware about the disease and the probable consequences of the medication non-adherence. Education status was significantly associated with medication adherence as education and knowledge is the most preliminary things for the patients to be more aware about the disease and adherence. Educated patients were more adhered to medication than those who cannot read and write because some of the patients who cannot read and write might didn't know about the disease condition that they were suffering, so they thought the disease condition might easily be cured with the regular used of the medications. A number of socio-demoghraphic like sex, and yearly income were found to significantly associated with non-adherence [30]. But in this study were not associated statistically significant,the reason behind this variation might be due to the sample size and methodological difference.

In this study, patients with poor medication adherence reported different reasons for non-adherence. The most common reason for the non-adherence was the high cost of the medications which is in agreement with same study conducted by Bhupendra Verma *et al*, in India [48]. Non-adherence due to cost of medication was more in patients, some of the medications like erythropoietin have high cost that medium income people couldn't afford. Likewise torsemide prescribed by the physicians was also costed high. This might be due to the lack of pharmacoeconomic evaluations and vigilance in the hospital.

5. Conclusion

This study was conducted to find out the prevalence of medications used in the management of CKD, level of adherence (high, medium and poor) and the reasons of medication non-adherence. In summary, 85% of hypertensive the hypertensive patients were treated with non-ACEIs. Insulin and non-ACEIs based regimens were prescribed mostly to treat diabetes mellitus and hypertension. Insulin alone was prescribed predominately for Diabetes mellitus alone. Only 32.9% of the patients were adhered highly to the prescribed, which was recognized as sub-optimal. High cost of medication 51% was found to be the main reason for medication non-adherence. Age group below 65 years, occupations and education status were the significantly associated with the medication adherence.

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