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RESEARCH ARTICLE

PRESCRIPTION OF RENIN-ANGIOTENSIN SYSTEM BLOCKERS AND RISK OF HYPERKALEMIA IN PATIENTS WITH DIABETES MELLITUS: RETROSPECTIVE STUDY

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ABSTRACT

The development of hyperkalemia is thought to be significantly associated with the use of ACE inhibitors andARBs. A retrospective observational cohort study conducted was conducted with200 in patients among the study subjects of the age group of 18 years and above. Majority of the cases were males (50.5%) than females (49.5%). Average serum potassium of non-exposed group was found to be 3.9±0.36 mEq/L and exposed group was found to be 4.1±0.5 mEq/L. Average baseline creatinine(mg/dL) of non-exposed group was 1±0.82 mg/dL and exposed group was 0.96 ±0.2 mg/dL. ACEIs were administrated to 1% of the patients (1/100) and ARBs to 99% (99/100). Incidences of hyperkalemia were the highest with the use of losartan (0.92%,2/13), olmesartan (0.85%, 2/14) followed by telmisartan (0.64%, 7/65 persons). The causality assessment of reported ADRs as per the Naranjo scale revealed that 67% were probable, 33% were definite, 0% were possible and unlikely. The Hartwig severity scale showed that all were of mild type and according to the modified Schumock and Thornton scale all were probably preventable there was a significant association between Hyperkalemia and administration of ARBS/ACE –inhibitors ($\chi 2$= 11.640, df= 2, $p<0.01$).

Citation: ***Akshitha D Ajay, Gini C Johns, Mareena Mathew, Athira, S. and Cijo George.*** **2023.** "Prescription of renin-angiotensin system blockers and risk of hyperkalemia in patients with diabetes mellitus: retrospective study*". International Journal of Current Research*, 15, (02), xxxx-xxxx

INTRODUCTION

The hormone system known as the renin-angiotensin-aldosterone system controls systemic vascular resistance, fluid and electrolyte balance, and blood pressure. Following treatment with angiotensin-converting enzyme inhibitors, hyperkalemia is frequently noticed. Aldosterone is reduced by ACE inhibitors, which may also result in higher serum potassium levels. Patients with CKD or those who are simultaneously taking potassium supplements, potassium-sparing diuretics, ARBS, or a direct renin inhibitor are more likely to develop hyperkalemia. Hyperkalemia frequently manifests as cardiac dysrhythmias, fatigue, disorientation, cramping in the muscles, and shortness of breath. Both intracellular potassium release and failure of the excretory route contribute to the elevated potassium levels. [1]

MATERIALS AND METHOD

A retrospective study was conducted among the in-patients admitted to SH Medical Centre hospital, a tertiary care hospital in Kerala, India. The patient records admitted in cardiology, nephrology and general medicine department were collected of patients having type 2 diabetes mellitus and hypertension. Data such as demographic characteristics, symptoms and its duration, comorbidities, and clinical parameters like blood pressure were collected. Laboratory parameters such as serum creatinine, serum potassium, GRBS, FBS, PPBS, HbA1c were collected for both exposed and control study subjects.The data of patients having antihypertensives ACEIs and ARBs were also collected.For the determination of causality assessment of reported ADRs was done as per the Naranjo scale and severity was assessed by Hartwig severity scale. This data in this study belongs to patients who have already been discharged and which was collected at the end of the treatment, so this study is not in a violation of the rights and interests of the participants and has little impact on their mental or physical health. The study was approved by the IEC of the SH Medical Centre, Kottayam. Therefore, informed consent was not required

STATICAL ANALYSIS: A retrospective study was conducted among the in-patients admitted to hospital. The data of patients having antihypertensive ACEIs and ARBs were also collected. Descriptive statistics was used to summarize variable demographic parameters and study objectives. Discrete variables were tabulated and chi square test were used to analyze it.

A p value of <0.05 was considered as significant. Karl Pearson's coefficient of correlation was used to correlate Serum potassium, age, sex, duration of use, BMI , blood pressure. Chi square was used to find the association of hyperkalemia with administration of renin angiotensin system blockers.

RESULT AND DISCUSSION

GENDER

Table 1

GENDER	FREQUENCY	RELATIVEFREQUENCY(%)
MALE	101	50.5
FEMALE	99	49.5
	N=200	100

Table 1 it shows that, in our study containing a total of 200 cases majority of the patients were males (50.5%), followed by females (49.5%). Other studies [6,9] also have the similar results.

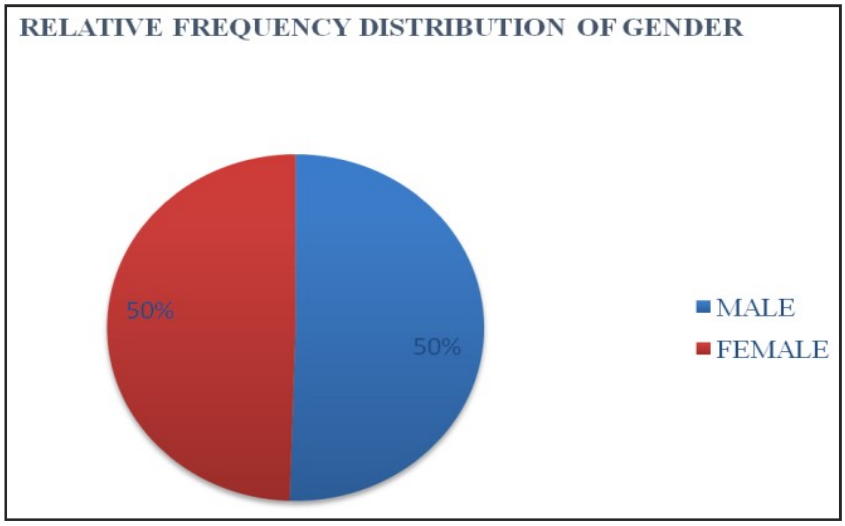


Figure 1

Table 2

GENDER	EXPOSED	NON EXPOSED	TOTAL (N=200)	RELATIVE FREQUENCY(%)
MALE	40	61	101	50.5
FEMALE	60	39	99	49.5
	100	100	200	100

Table 2 shows that out of 200 patients ,40 were male and 60 were female in exposed group and 61 were male and 39 were female in non-exposed group. The relative frequency was found to be 50.5% for male and 49.5% for female.Other studies [6,9] also have the similar results.

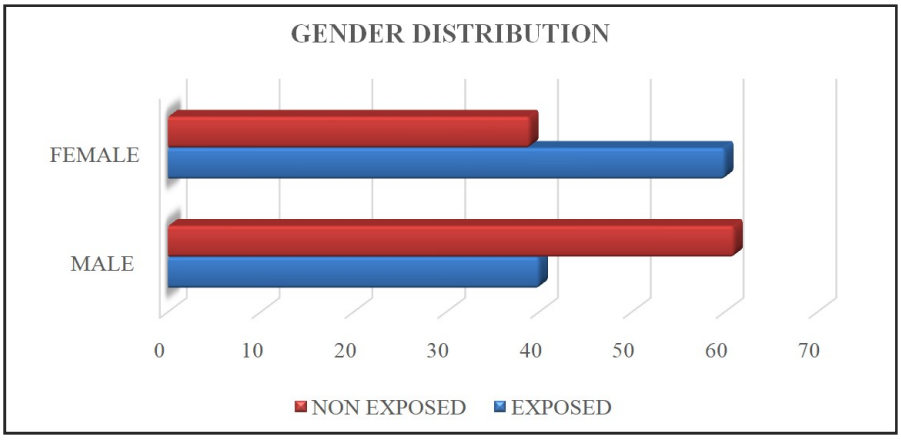


Figure 2

The gender distribution in exposed and non-exposed group is depicted in figure 2

AGE

Table 3.

AGE (N=200)	NON EXPOSED	EXPOSED	TOTAL	RELATIVE FREQUENCY (%)
≤50	4	3	7	3.5%
51-59	21	26	47	23.5%
60-70	45	27	72	36%
71-79	14	28	42	21%
≥80	16	16	32	16%
	100	100	200	100

The average age of patients in the non-exposed group was 62 ± 13 years and 68 ± 11 years in the exposed group. The table 3 demonstrates that from a total of 100 cases, the majority of the patients (71%) were in the age group of 60 years above, which was consistent with prior reports in the literatures [6,7,8,9] Relative frequency distribution of age groups is depicted in figure 3.

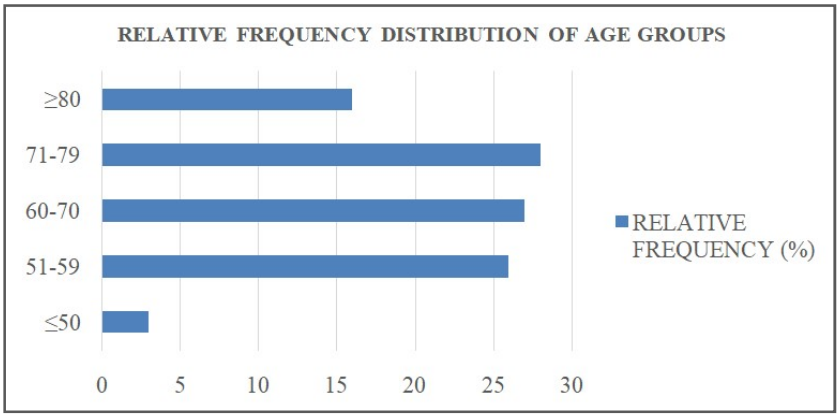


Figure 3

Age groups distribution in exposed group is depicted in figure 4

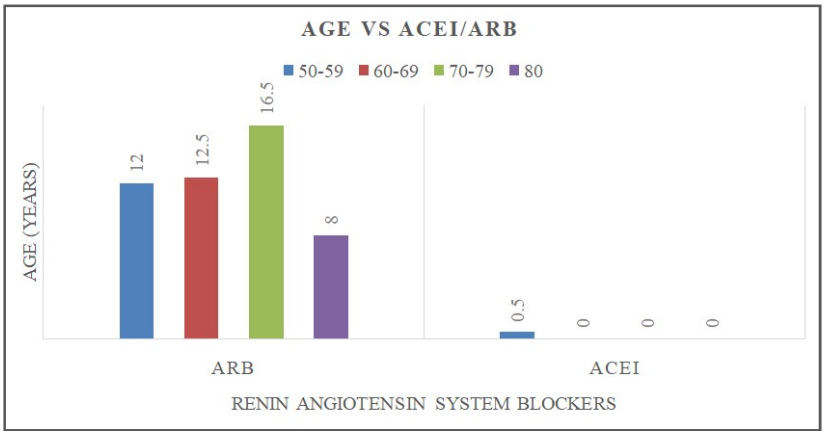
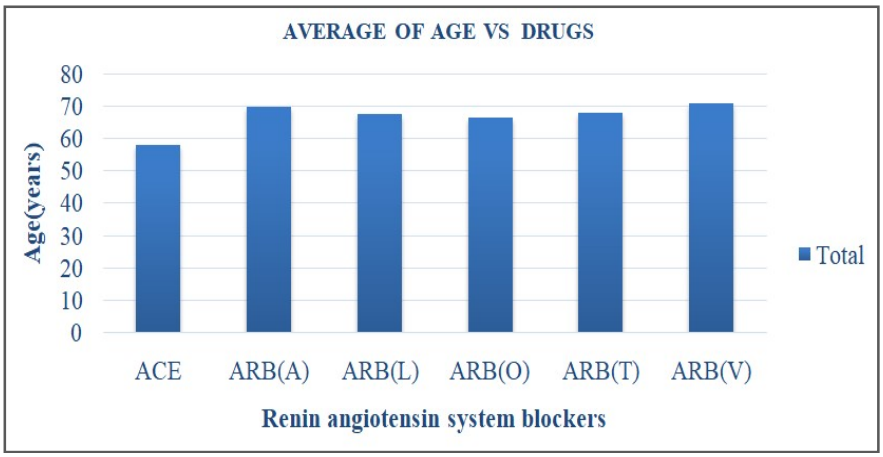


Figure 5 represents renin angiotensin receptor blockers and their average age distribution



COMORBIDITIES

Table 4.

COMORBIDITIES (N=200)	NON EXPOSED	EXPOSED	TOTAL	RELATIVE FREQUENCY (%)
Ischemic heart disease	1	11	12	6 %
COVID 19	8	27	35	17.5 %
CAD	5	15	20	10%
CVA	5	7	12	6%
CHF	25	1	26	13%
Infections	0	21	21	10.5%

The table 4 demonstrates that from a total of 200 cases, the majority of the patients had COVID 19 (17.5%)

Figure 6 represents comorbidities in exposed group and in non-exposed group

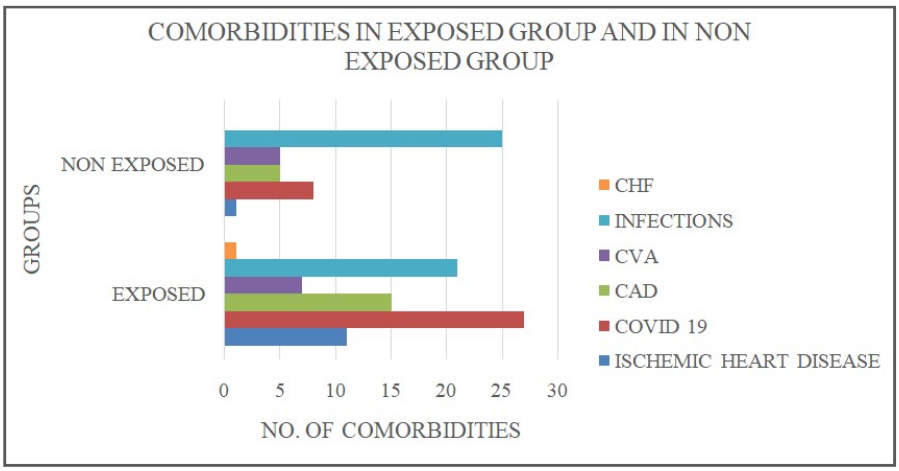


Figure 6

BASELINE CHARACTERISTICS

Table 5.

PARAMETER (N=100)	VALUE (Mean ± Std.dev)
Average Serum Creatinine (mg/dL)	1.3±0.6
Average serum potassium (mEq/L)	4.1±0.5
Average baseline creatinine(mg/dL)	0.96 ±0.2
Systolic Blood Pressure (mmHg)	136.7±13.56
Diastolic Blood Pressure (mmHg)	81.6±7.74
BMI (kg/m^2)	24.6±2.3

Table 6.

PARAMETER (N=100)	VALUE (Mean ± Std.dev)
Average Serum Creatinine (mg/dL)	1.0±0.56
Average serum potassium(mEq/L)	3.9±0.36
Average baseline creatinine(mg/dL)	1±0.82
Systolic Blood Pressure (mmHg)	141.05±14.32
Diastolic Blood Pressure (mmHg)	82.5±8.35
BMI (kg/m^2)	24.1±3.37

Table 5 represents baseline characteristic of exposed group and table 6 represents baseline characteristics of non- exposed group which was consistent with prior reports in the literatures [6,7,8,9]

DISTRIBUTION OF RENIN ANGIOTENSIN SYSTEM BLOCKERS

Table 7

PARAMETER (N=100)	FREQUENCY AND RELATIVE FREQUENCY
ARBs	99 (99%)
ACEIs	1 (1%)

Table 7 shows that out of 100 cases, ACEIs were administrated to 1% of the patients (1/100) and ARBs to 99% (99/100) which was not consistent with prior reports in the literatures [6,7,8,9]. This may be due to the increase potential to cause adverse events induced by ACEIs.

Figure 7 represents the renin angiotensin system blocker users

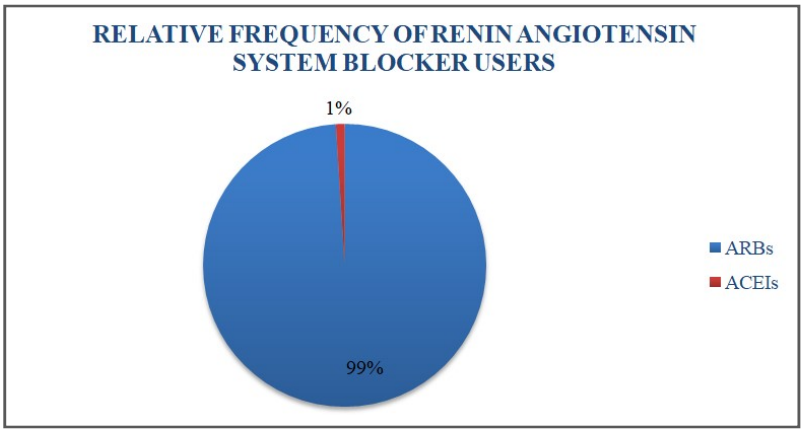


Figure 7.

BMI

Table 8.

BMI (N=100)	FREQUENCY	RELATIVE FREQUENCY (%)
<18	0	0
18-24.99	55	55
25-29.99	44	44
≥ 30	1	1
	100	100

Table 8 depicts Relative Frequency of BMI of Exposed group. The BMI of patients was 24.1±3.7 kg/m^2 in the non-exposed group and 24.6±2.3 kg/m^2 in the exposed group which was consistent with prior reports in the literatures [6,7,8,9].

Figure 8 represents the relative frequency of BMI

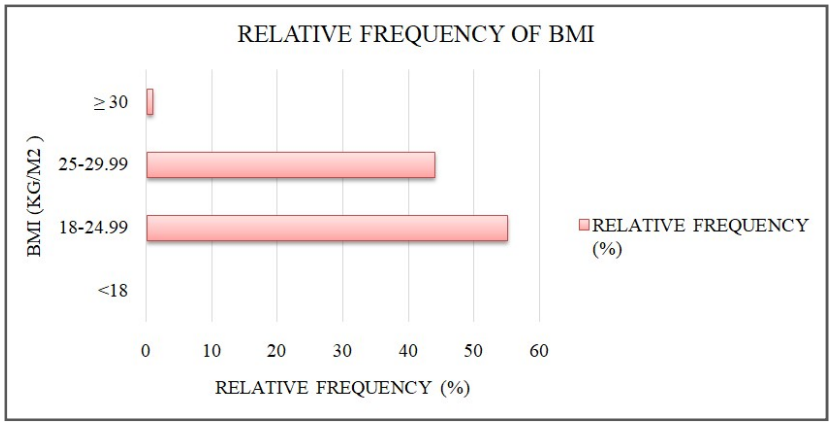


Figure 8

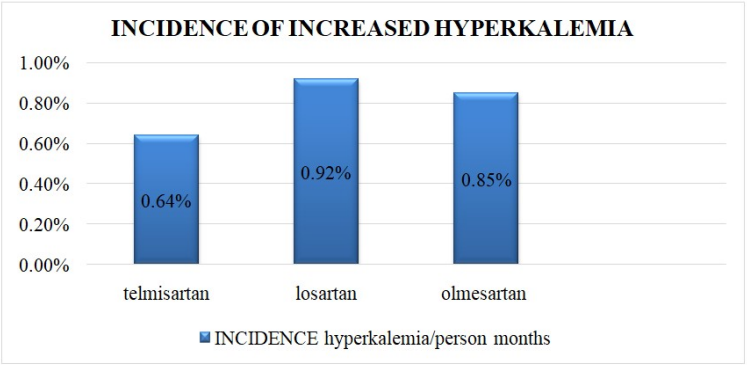


Figure 9

SERUM HYPERKALEMIA

Figure 9 represent the incidence of hyperkalemia and the highest incidence of hyperkalemia according to the ARB type was associated with the use of telmisartan 10.7% (7/65 exposed), and olmesartan 14.2% (2/14 exposed), losartan 15.38% (2/13 exposed) at the 5.5 mEq/L potassium standard. Incidence of hyperkalemia were the highest with the use of losartan (0.92%, 2/13), olmesartan (0.85%, 2/14) followed by telmisartan 0.64% (7/65 persons), which was similar to study of Hye-Ran Jun et al [9]

Figure 10 represents renin angiotensin receptor blockers and their average serum potassium

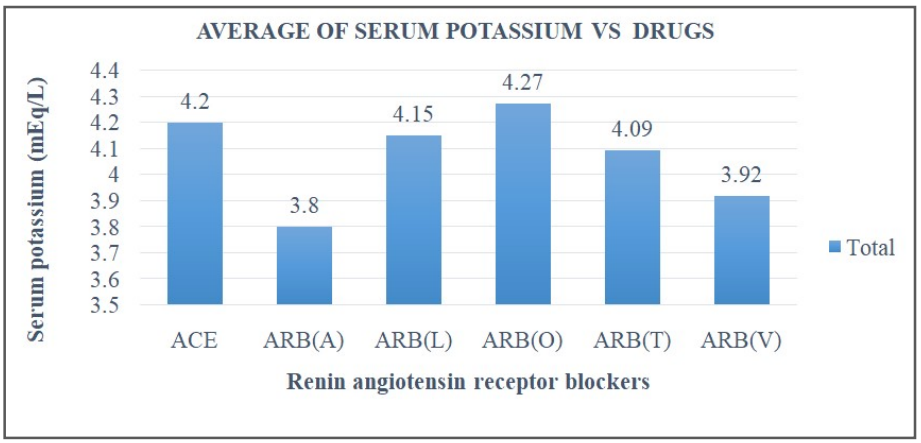


Figure 10.

Table 9 represents the various drugs that caused hyperkalemia where telmisartan (63.63%) caused highest percentage of ADR followed by olmesartan (18.18%) and Losartan(18.18%).

Table 9.

CLASS OF DRUG	NAME OF DRUGS	NO. OF ADR	% OF ADR
ANGIOTENSIN RECEPTOR BLOCKERS	Telmisartan	7	63.63%
	Olmesartan	2	18.18%
	Losartan	2	18.18%

Table 10.

Drug	DosageForm	Reaction	NARANJO	Severity	Preventability
Telmisartan	Oral	Hyperkalemia	Definite	Mild	Probably Preventable
Olmesartan	Oral	Hyperkalemia	Probable	Mild	Probably Preventable
Losartan	Oral	Hyperkalemia	Definite	Mild	Probably Preventable

Table 10 shows that, an assessment of ADR by Naranjo causality assessment scale showed possible ADR among the patients. Preventability of ADRs was assessed using the modified Shumock and Thornton method. Using the scale, results revealed that all ADRs were Probably preventable which was parallel to study Jun R H et al [9] Figure 11 shows the causality assessment of reported ADRs as per the Naranjo scale and revealed that 67% were probable, 33% were definite, 0% were possible and unlikely.

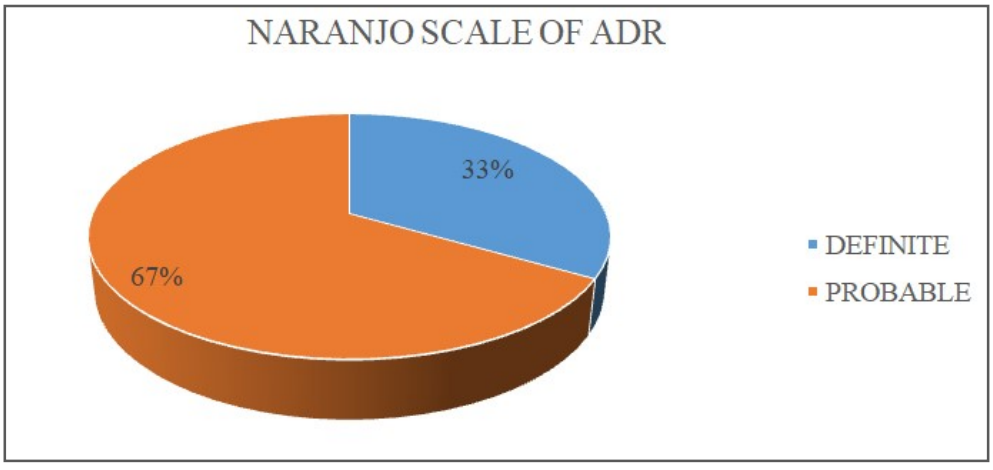


Figure 11.

HYPERKALEMIA VS RENIN ANGIOTENSIN SYSTEM BLOCKERS

Table 11.

ADR (N=100)	FREQUENCY AND RELATIVE FREQUENCY		χ^2 test
	Exposed (N=100)	Not-exposed (N=100)	
Nil	89 (44.5%)	100(50%)	$\chi^2 = 11.640$, df= 2 , p= 0.003** **Significant at 0.01 level
Definite	3(1.5%)	0	
Probable	8(4%)	0	

Data presented in table 11 revealed that there was a significant association between Hyperkalemia and administration of ARBS/ACE –inhibitors ($\chi 2$= 11.640, p<0.01) which was similar to study of Agustina PS et al. [10]with p =0.028. Data presented in table 12 revealed that there was a significant association between presence of ADR and age in years ($\chi 2$= 10.289, df= 4, p= 0.036*) which was similar to study of Agustina PS et al. [10] with p =0.028

Figure 12 representscausality assessment of ADR and administration of ARBS/ACE –inhibitors

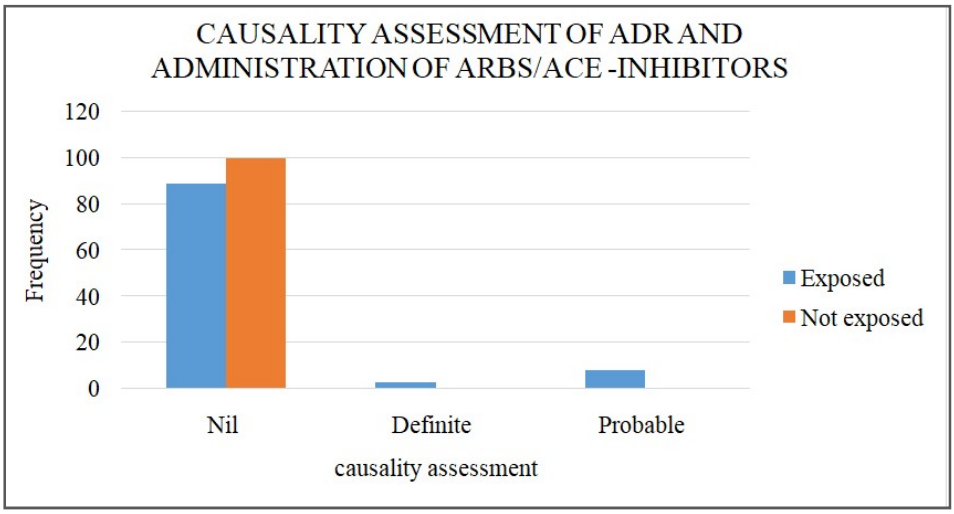


Figure 12.

ASSOCIATION OF HYPERKALEMIA WITH AGE IN YEARS

Table-12

Age in years (N=100)	ADR		χ^2 test
	Absent	Present	
≤50	3(1.5%)	0	$\chi^2 = 10.289$, df= 4, p= 0.036* *Significant at 0.05 level
51-60	26 (13.0%)	0	
61-70	24(12.0%)	3 (1.5%)	
71-80	25(12.5%)	3(1.5%)	
>80	11(5.5%)	5(2.5%)	

Figure 13 depicts the frequency of ADR in various age groups.

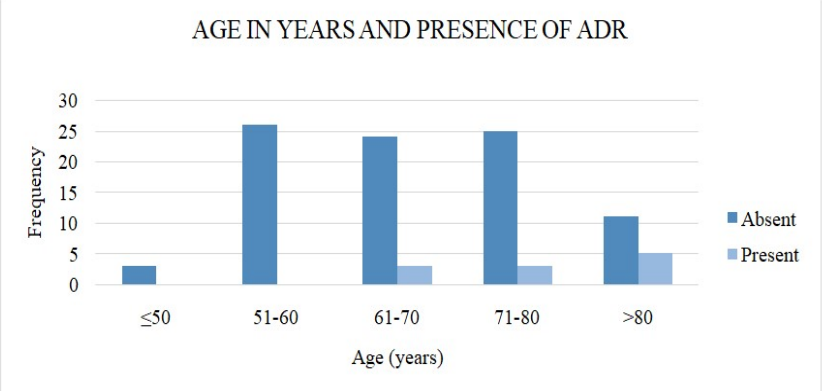


Figure 13

ASSOCIATION OF HYPERKALEMIA WITH GENDER

Table 13.

Sex	ADR		χ^2 test
	Absent	Present	$\chi^2 = 0.153$, df= 1, p= 0.695 (NS)
Male	54(27.0%)	6(3.0%)	
Female	35(17.5%)	5(2.5%)	

Data presented in table 13 revealed that there was no significant association of Hyperkalemia and sex ($\chi2$= 0.153, df= 1, p= 0.695) which was similar to study of Agustina PSet al. [10] with p =0.86. Figure 14 depicts the frequency of hyperkalemia in sex

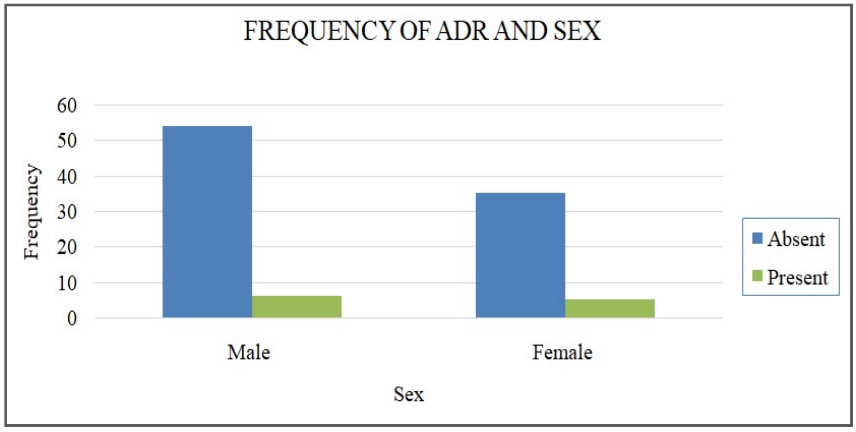


Figure 14.

ASSOCIATION OF HYPERKALEMIA WITH DURATION OF DRUG USE

Duration of drug use (months) N=100	FREQUENCY OF ADR		χ^2 test
	Absent	Present	
≤5	14(7.0%)	1(0.5%)	χ^2= 1.936, df= 3, p= 0.586 (NS)
6-10	40(20.0%)	7(3.5%)	
11-15	28(14.0%)	3(1.5%)	
>16	7(3.5%)	0	

Data presented in table 14 revealed that there was no significant association of Hyperkalemia and duration of drug use ($\chi2$= 1.936, df= 3, p= 0.586) which was similar to study of Agustina PS et al. [10] p = 0.056.

Figure 15 represents duration of drug use and hyperkalemia

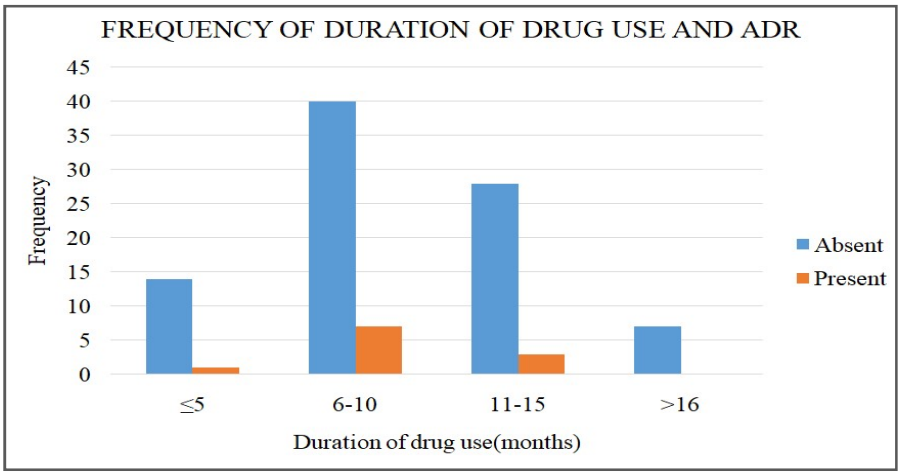


Figure 15

ASSOCIATION OF HYPERKALEMIA WITH BMI

Table 15.

BMI (kg/cm^2) (N=100)	**ADR**		**$\chi2$ test**
	Absent	Present	
<18	-	-	χ^2 = 1.616, df= 2, p= 0.446 (NS)
18-24.99	47(23.5%)	8(4%)	
25-29.99	41(20.5%)	3(1.5%)	
≥ 30	1(0.5%)	0	

Data presented in table 15 revealed that there was no significant association of Hyperkalemia and BMI ($\chi 2$= 1.616, df= 2, p= 0.446) which was similar to study of Agustina PSet al. [10]p = 0.056

Figure 16 represents hyperkalemia with BMI

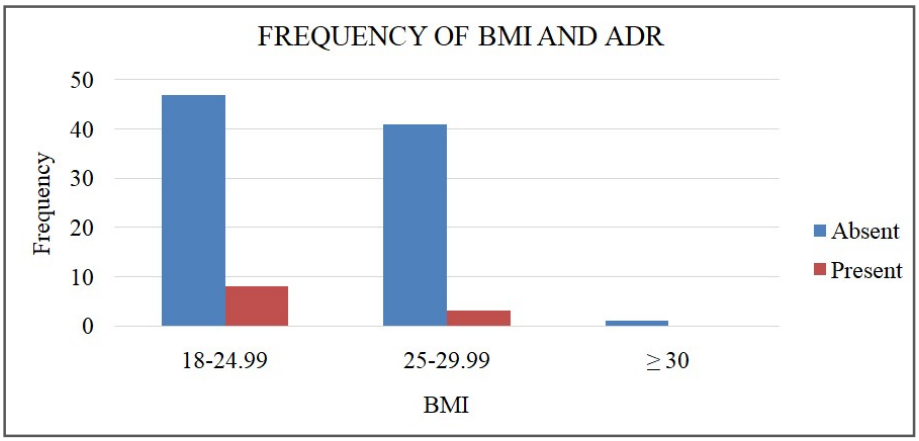


Figure 16

ASSOCIATION OF HYPERKALEMIA WITH SYSTOLIC BLOOD PRESSURE

Table 16.

Systolic BP (mmHg) N=100	ADR		χ^2 test
	Absent	Present	
≤120	16(8.0%)	5(2.5%)	χ^2 = 1.008, df= 2, p= 0.799 (NS)
121-140	51(25.5%)	2(1%)	
141-160	21(10.5%)	4(2%)	
>160	1(0.5%)	0	

Data presented in table 16 revealed that there was no significant association of Hyperkalemia and Systolic Blood Pressure (χ^2= 1.008, df= 2, p= 0.799) which was similar to study of Agustina PSet al. [10] of p = 0.056

Figure 17 represents frequency of hyperkalemia and systolic blood pressure

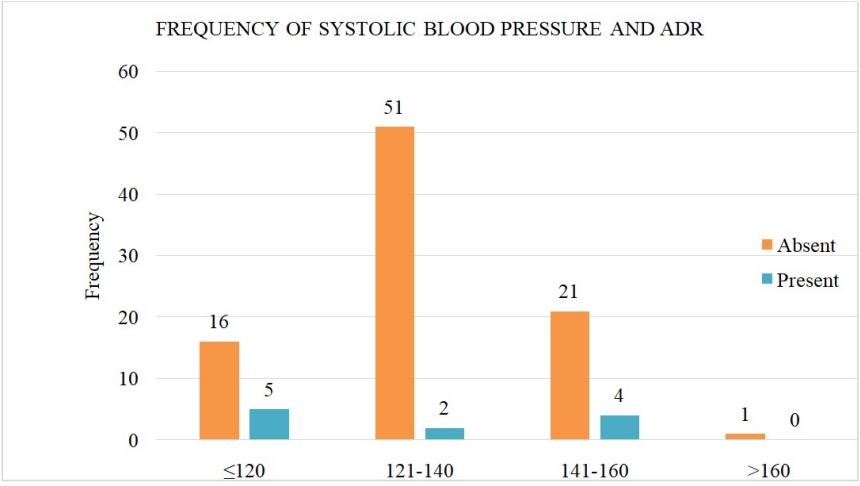


Figure 17

ASSOCIATION OF HYPERKALEMIA WITH DIASTOLIC BLOOD PRESSURE

Diastolic BP N=100	ADR		χ^2 test
	Absent	Present	
≤80	69(34.5%)	8(4%)	χ^2 = 0.143, df= 2, p= 0.931 (NS)
81-90	14(7%)	2(1%)	
>90	6(3%)	1(0.5%)	

Data presented in table 17 revealed that there was no significant association of Hyperkalemia and DiastolicBlood Pressure (χ^2 = 0.143, df= 2, p= 0.931) which was similar to study of Putri S. Agustina et al.[10] of p =0.056

Figure 18 represents frequency of diastolic blood pressure and hyperkalemia

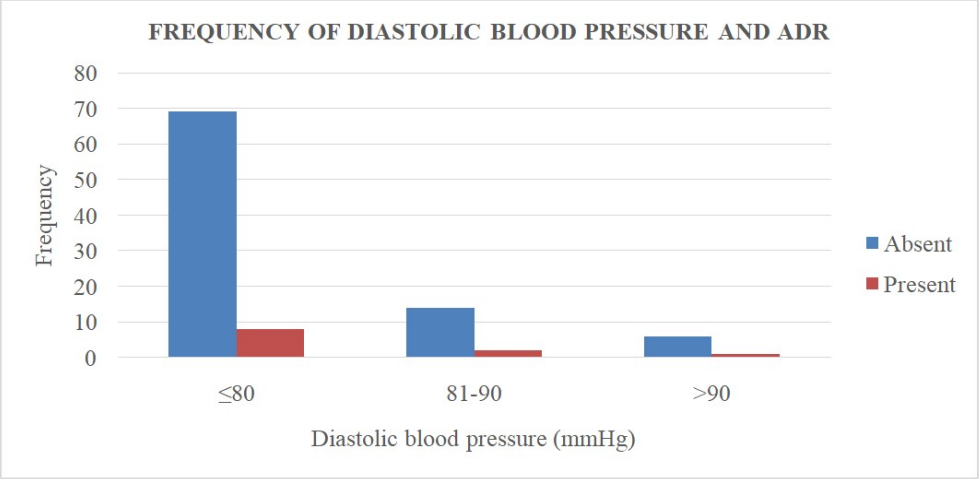


Figure 18

CORRELATION OF SERUM CREATININE WITH SERUM POTASSIUM

Variables	Mean	SD	r value	p value	Type of correlation
Creatinine level	1.17	0.65	0.618	<0.001***	Moderate positive
Potassium level	4.18	0.60			

Data presented in table 18 revealed that there was significant moderate positive correlation of creatinine level and Potassium level among samples exposed to ARBs/ACE inhibitors which was similar to study with prior reports in the literatures[6,7,8,9].

Figure 19 depicts Scatter diagram representing moderate correlation of creatinine level and Potassium level among samples exposed to ARBS/ACE inhibitors

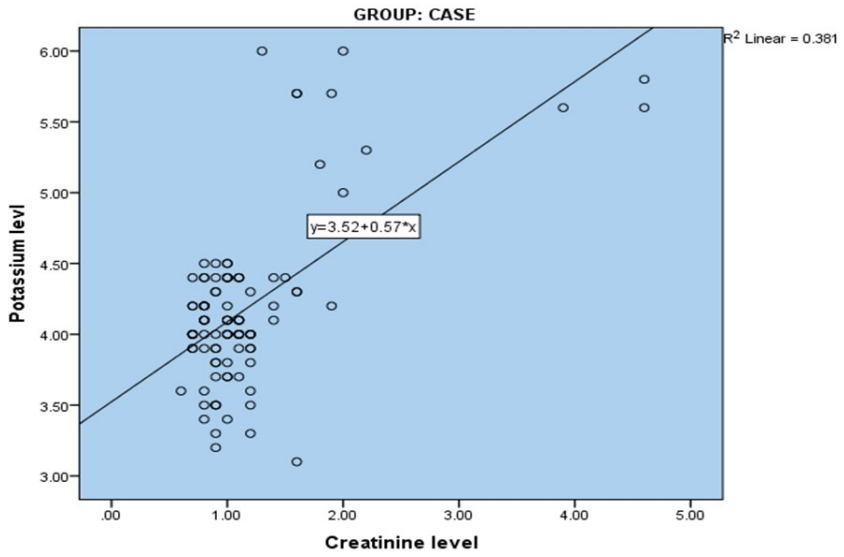


Figure 19

Data presented in table 19 revealed that there was low positive correlation of creatinine level and Potassium level among samples not exposed to ARBs/ACE inhibitors which was similar to study with prior reports in the literatures [6,7,8,9].

Table 19.

Variables	Mean	SD	r value	p value	Type of correlation
Creatinine level	1.09	0.57	0.003	0.979 (NS)	Low positive
Potassium level	3.99	0.36			

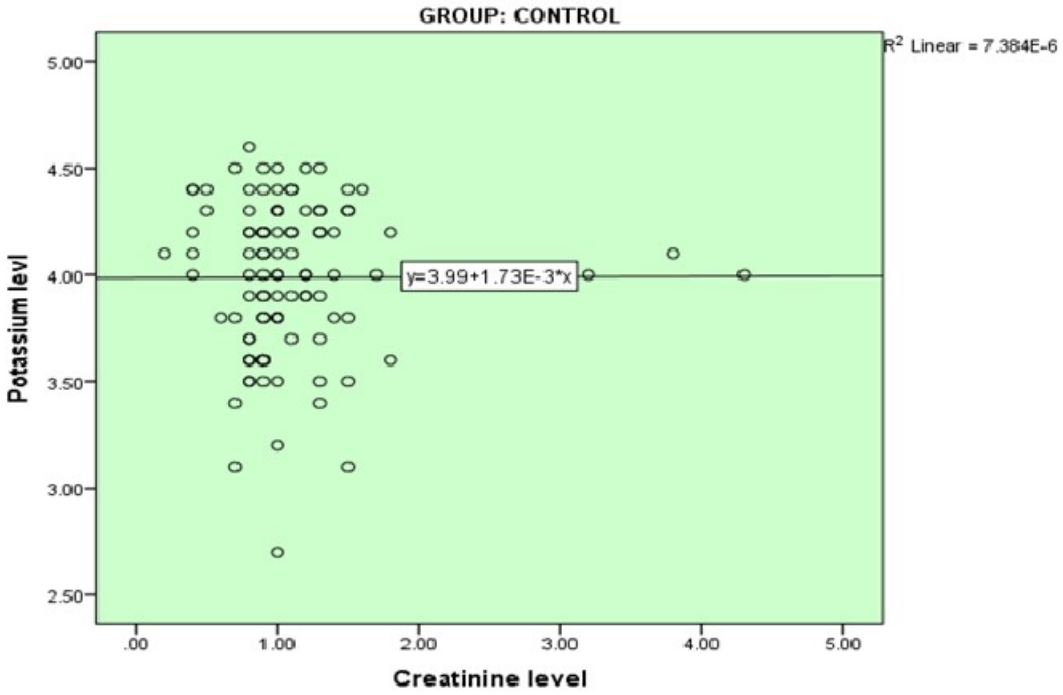


Figure 20

Figure 20 depicts the Scatter diagram representing low positive correlation of creatinine level and Potassium level among samples not exposed to ARBS/ACE inhibitors

CONCLUSION

A total of 100 patients' prescriptions were studied to evaluate if there was a risk of hyperkalemia associated with renin-angiotensin system blockers along with patient demographics, length of hospital stay. Our study helped to understand most commonly seen comorbidities and understand the risk of hyperkalemia and the adverse drug reaction associated and its severity in diabetes mellitus. A total of 11 (5.5%) patients with hyperkalemia were found associated with the use of renin-angiotensin system blockers. The association of hyperkalemia induced by angiotensin receptor blockers were found to be statistically significant. On the other hand, there was no significant association with age, sex, duration of use, BMI, systolic and diastolic blood pressure. All of the adverse drug reactions were of mild severity and probably preventable respectively according to Hartwig's severity scale and preventability criteria assessed by modified Schumock and Thornton scale. ADRs are common occurrence but they are not often recognized. Even if they are recognized they are underreported as many are unaware about the clinical importance. The clinical pharmacist can provide their services by doing clinical interventions, inspecting patient care area and nursing station regarding use of renin angiotensin system blockers. Therefore, Implementation of multidisciplinary healthcare team including clinical pharmacist (Pharm D) will be beneficial to achieve the rational use of medicine, increase patient safety.

LIMITATIONS

- It was a retrospective study.
- This study was conducted in a short term duration, having small sample size and conducted in a single center.
- Only one patient was included in the study having ACEI as practitioners preferentially prescribe ARBs over ACEIs
- Patients are studied only while they are hospitalized. Therefore, any complications occurring after patients' discharge from their wards were not documented.
- Do not provide any information on the time frame of development of hyperkalemia

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