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Research Article

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Study of Prescription Pattern of Oral Hypoglycemic Agents in Relation to Gfr Appropriateness in Diabetes Mellitus with Nephropathy

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ABSTRACT

Aim: *The decline in the renal function impairs the clearance and metabolism of the anti-diabetic agents and insulin, resulting in the frequent requirement of the prescription reassessment.*

Objective:*The objective is to sort out the inappropriateness in the prescription pattern of oral hypoglycemic agents in diabetes mellitus with nephropathy.*

Method:*The prescriptions were randomly selected for the study, after they fulfilled the necessary inclusion, exclusion criteria. After obtaining the informed consent form, the socio demographic data, details of anti-diabetic therapy, required laboratory investigations (serum creatinine, BUN, BUN:Se.cr ratio, CUE, HbA1C), hypoglycemic episodes (if any) are recorded. Another required parameter GFR is calculated using CKD-EPI equation. Fischer exact test is used to test the significance of hypoglycemic episodes among CKD 1-2 and CKD 3-5.*

Results:*Metformin+Glimepiride combination is the most commonly prescribed medication (34.6%), followed by metformin alone (23.07%). The drugs which are found to be least prescribed are Glipizide (1.92%), Sitagliptin (1.92%), Pioglitazone (0.96%). Inappropriately prescribed drug which is highly responsible for hypoglycemic episodes is Metformin+Glimepiride (22.22%).*

Conclusion:*Biguanides and sulphonylureas have been found to dominate the prescription pattern of DM-II, despite of the presence of the comorbidity such as nephropathy.*

Keywords: Diabetes mellitus; Hypoglycemia; Nephropathy; Inappropriateness; Prescribing pattern; Oral hypoglycemic agents; Decreased GFR; CKD; Neuroglycopenia

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INTRODUCTION

As the title itself suggests, the study mainly focuses on the prescription pattern of the oral hypoglycemic agents by the dialectologists, nephrologists and other health care practitioners.

The purpose behind the initiation of this study is to sort out the inappropriateness in the prescription pattern of oral hypoglycemic agents in diabetes mellitus with nephropathy, so that based on the results a better, appropriate treatment regimen can be obtained which helps in better glycemic control with fewer complaints of hypoglycemic episodes.

Diabetes treatment in patients with diabetic kidney disease is challenging in part, because of progression of renal failure-related changes in insulin signaling, glucose transport and metabolism, favoring both hyperglycemic peaks and hypoglycemia. Additionally, the decline in renal function impairs the clearance and metabolism of anti-diabetic agents and insulin, frequently requiring reassessment of prescriptions. The management of hyperglycemia in patients with diabetic kidney disease is even more difficult, requiring adjustment of anti-diabetic agents and insulin doses [1].

Many oral hypoglycemic drugs have renal metabolism and their metabolites are usually active prolonging their time of action. These active metabolites are retained in the body for long time in case of decreased GFR and cause hypoglycemia. Severe hypoglycemic episodes can prove fatal. The major problem is that in many efficacy studies, patients with CKD are excluded so data of safety and efficacy for these patients are missing. This results in fear of

use by lack of evidence. Finally, the use of anti-diabetic drugs is more complicated in these patients, because many people with kidney disease are often elderly, and have long lasting disease and significant co-morbidities. These people take many drugs and they have high risk of drug interactions [2].

LITERATURE REVIEW

Allen Meeme and Hannington Kasozi in their study
"Effect of glycaemic control on glomerular filtration rate in diabetes mellitus patients"
using a paired sample t-test and p-value set at 0.05 (95% CI) concluded that a reduction in GFR reflects reduction of hyper filtration, a process that starts diabetic nephropathy. Good glycemic control will go a long way to delay onset of diabetic nephropathy [3].
André J Scheen in his study
"Pharmacokinetic considerations for the treatment of diabetes in patients with chronic kidney disease"
concluded that in case of metformin and sulphonylureas the daily dose should be reduced according to glomerular filtration rate (GFR) or even the drug is contraindicated in presence of severe CKD. New anti-diabetic agents are better tolerated in case of CKD, although clinical experience remains quite limited for most of them. The dose of DPP-4 inhibitors should be reduced (except for linagliptin), whereas both the efficacy and safety of SGLT2 inhibitors are questionable in presence of CKD [4].
Carolina C R Betônico Silvia M O Titan et.al in their study
"Management of diabetes mellitus in individuals with chronic kidney disease: therapeutic perspectives and glycemic control"
concluded that the decline in renal function impairs the clearance and metabolism of anti-diabetic agents and insulin, frequently requiring reassessment of prescriptions. The management of hyperglycemia in patients with diabetic kidney disease is even more difficult, requiring adjustment of anti-diabetic agents and insulin doses [5].
Ning Wu et.al in their study
"Evaluation of the prevalence of chronic kidney disease and rates of oral antidiabetic prescribing in accordance with guidelines and manufacturer recommendations in type 2 diabetic patients within a long-term care setting"
concluded that PI nonconcordance was observed in 58.6% of residents and was highest in glipizide and metformin users. With the high prevalence of moderate to severe CKD in NH residents with diabetes, physicians should consider residents' renal function when choosing treatment plans and review treatments regularly to check compliance with the NKF guidelines or PIs [6].
Meyers JL et.al in their study
"Type 2 diabetes mellitus and renal impairment in a large outpatient electronic medical records database: rates of diagnosis and antihyperglycemic medication dose adjustment"
concluded that patients with a documented RI diagnosis have lower odds of progression to end-stage RI. Metformin and sitagliptin are frequently used at inappropriate doses in patients with RI [7].

MATERIALS AND METHODS

This study is a retrospective, observational study carried out in the nephrology department of Kamineni hospitals Beside Big Bazar, Inner Ring Road, LB Nagar, after obtaining the required permission from the ethical committee. This study was carried out for the time period of six months (September 2017-February 2018) on the sample size of 104 prescriptions. The prescriptions were randomly selected for the study, after they fulfilled the necessary inclusion, exclusion criteria. After obtaining the informed consent form, the socio-demographic data, details of anti-diabetic therapy, required laboratory investigations (serum creatinine, BUN, BUN: Se.cr ratio, CUE, HbA1C), hypoglycemic episodes (if any) are recorded. Another required parameter GFR is calculated using CKD-EPI equation. The parameters which are analyzed are an average number of OHA per prescription, the percentage of different OHA prescribed, commonest class prescribed, the percentage of appropriate and inappropriate prescriptions, the relative frequency of CKD among the DM-II subjects enrolled for the study, the prevalence of hypoglycemic episodes among the subjects enrolled. The study data is analyzed using Microsoft Access 2010, Microsoft Excel 2010, with $P<0.005$ being considered as statistically significant. Fischer exact test is used to test the significance of hypoglycemic episodes among CKD 1-2 and CKD 3-5. The calculated data is expressed in terms of the actual number, percentages and mean value.

STUDY CRITERIA

Inclusion criteria

- Outpatients as well as inpatients
- Both the genders.
- Age 18-80
- Patients who are k/c/o type-II diabetes mellitus with nephropathy and are on oral hypoglycemic agents.
- Patients with other co-morbidities are also included.
- Patients with social history such as smoking, alcoholism are also considered.

Exclusion criteria

- Pregnant and lactating women.
- Diabetic patients on insulin
- Pediatrics

RESULTS

Figure 1: Prevalence of the Ckd Among the Study Participants

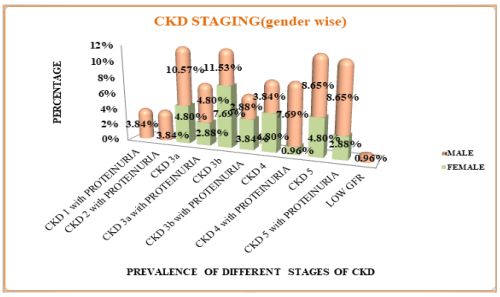

Figure 2: Proportion of Prescription Pattern of Oha

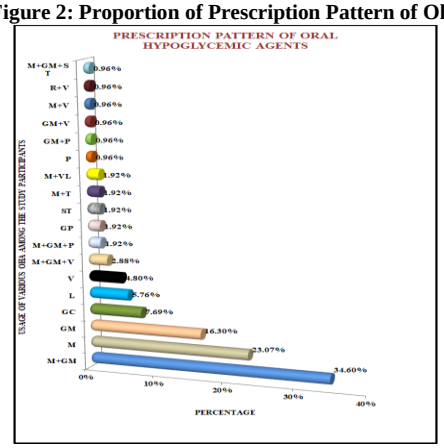

Figure 3: Observed Prescription Pattern of Oha in Nephropathy

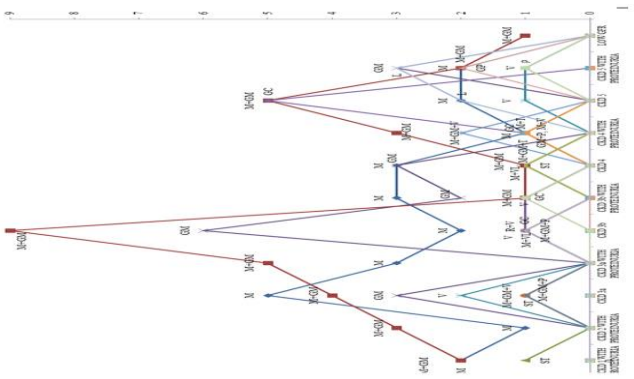

Figure 4: Prevalence of Hypoglycemic Episodes in Various Stages of Ckd

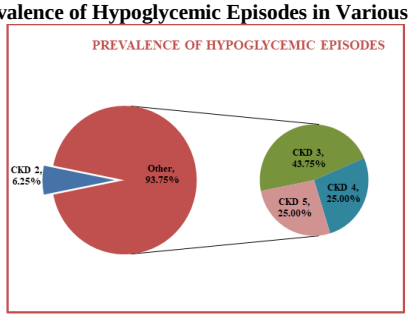

Table 1: Hypoglycemic Episodes Observed in Various Stages of ckd because of Oral Hypoglycemic

CKD stage	Number of Patients	Hypoglycemic Episodes
CKD 2	4	1
CKD 3-5	95	15
F- test two samples to variances		
	Hypoglycemic Episodes	
	CKD 2	CKD 3-5
Mean	2.5	55
Variance	4.5	3200
Observations	2	2
df	1	1
F	0.001406	
P(F<=f) one-tail	0.023862	
F critical one-tail	0.006194	

Table 2: Inappropriate Prescriptions Observed

Condition	Inappropriate prescriptions observed (based on literature review)	Mean ± SD	Inappropriate prescriptions observed (based on the study)	Mean ± SD
CKD 1 with proteinuria	0	5.45 ± 4.227	0	1.4545 ± 1.21
CKD 2 with	0		1	

proteinuria				
CKD 3a	6		1	
CKD 3a with proteinuria	6		3	
CKD 3b	13		3	
CKD 3b with proteinuria	2		0	
CKD 4	9		3	
CKD 4 with proteinuria	9		1	
CKD 5	7		2	
CKD 5 with proteinuria	7		2	
Lower GFR	1		0	

DISCUSSION

In this study we have attempted to describe the current prescribing pattern and trend of OHA in DM-II with nephropathy in maintaining an optimal glycemic level. The total number of subjects participated in the study are 104, of which males are 51.9% (IP) and 15.30% (OP) and females are 27.8% (IP), 4.6% (OP). Among the subjects considered for the study, the maximum number of subjects fall under the CKD stage 3b with a relative frequency of 19.23% (n=20) which is highly prevalent among sexagenarians and the minimum number of subjects fall under LOW GFR category with a relative frequency of 0.96%(n=1) [8-11]. Prevalence of comorbidities among the participants is found to be 75% [48.07% (n=50) in males and 24.03% (n=25) in females], with hypertension being the most common prevalent comorbidity having a relative frequency of 96% (n=72). For the study the total numbers of prescriptions evaluated are 104 and based on the evaluated data we are 95% confident that the mean of the anti-diabetic drugs per prescription 1.15 is in between the range of 0.86-1.37.[σ (1.299) (95% confidence interval)]. Out of total 104 prescriptions evaluated, the prescriptions with only OHA are 91.34 % (n= 95), and the prescriptions with OHA and insulin are 8.65% (n=9). Among the OHA prescribed, the percentage of combination drugs are 45.19% (n=47) and the percentage of drugs without combination are 54.8% (n=57). (Figure 1 and 2)Among the prescriptions evaluated for the study the following major prescription patterns observed are as follows [12].

Metformin+Glimepiride combination is the most commonly prescribed medication (34.6%), followed by metformin alone (23.07%). After Metformin, Glimepiride is the second most common drug prescribed (16.3%) followed by gliclazide (7.69%), linagliptin (5.76%), voglibose (4.80%). Apart from metformin and Glimepiride combination the following drugs are also prescribed in combination. Metformin+Glimepiride+Pioglitazone(2.88%),Metformin+Glimepiride+Voglibose(2.80%), Metformin+Tenegliptin (1.92%), Metformin+Vildagliptin (1.92%), Glimepiride+Pioglitazone(0.96%),Glimepiride+Voglibose(0.96%),Metformin+Voglibose(0.96%), Repaglinide+Voglibose (0.96%),Metformin+Glimepiride+Sitagliptin (0.96%) [13-16]. The combination of OHA is used to achieve better glycemic control. The following drugs are least prescribed Glipizide (1.92%), Sitagliptin (1.92%), and Pioglitazone (0.96%). Of all the subjects participated in the study only 9.61% (n=10) of the subjects have undergone glycated hemoglobin test, of which 44% (n=4) had good glycemic control and 33% (n=3) have poor glycemic control despite of appropriate OHA prescription (Figure 3 and 4). In this study all the drugs are prescribed by brand names which suggest the popularity of the brands among the health care practioners (Table 1 and 2) [17].

OBSERVED PRESCRIPTION PATTERN OF OHA IN NEPHROPATHY

The highly prescribed OHA in LOW GFR condition is metformin+glimepiride, in CKD 1 WITH PROTEINURIA is metformin, metformin+glimepiride combination, CKD 2 WITH PROTEINURIA is metformin+glimepiride, CKD 3a is metformin, CKD 3a WITH PROTEINURIA is metformin+glimepiride, CKD 3b is metformin+glimepiride, CKD 3b WITH PROTEINURIA is metformin, CKD 4 is metformin and glimepiride, CKD 4 WITH PROTEINURIA is metformin+glimepiride, CKD 5 is metformin+glimepiride, gliclazide, CKD 5 WITH PROTEINURIA is glimepiride, linagliptin [18,19].

The prevalence of hypoglycemic episodes among the subjects participated in the study is found to be 15.38% [males 8.65% (n=9), females 6.73% (n=7)] and is highly prevalent in CKD stage 3 and the major cause of the prevalence is decreased GFR in CKD. Prevalence of hypoglycemic episodes (n=16) in CKD 2 stage is 6.25% (n=1) and in CKD 3- 5 is 93.75% (n=15). This clearly indicates that as the GFR decreases the chances of encountering hypoglycemic episodes in a type-II DM patient with renal impairment increases. Therefore the doses of the oral hypoglycemic episodes have to be adjusted based on the renal functioning to prevent neuroglycopenia. The P value for the prevalence of hypoglycemic episodes in various stages of CKD calculated using FISCHER EXACT TEST was found to be statistically significant (p=0.02) [20].

Of all the prescriptions (n=104) evaluated for the study 84.61% (n=88) prescriptions are appropriate, 15.3% (n=16) prescriptions are inappropriate. Based on the evaluated data, we are 95% confident that the mean inappropriateness of the prescription 1.4545 lies in between the range of 0.737-2.1717 [σ (1.21) (95% confidence interval)].

Of the commonly prescribed OHA, metformin +glimepiride, metformin, glimepiride prescriptions are highly appropriate, whereas linagliptin prescriptions are totally appropriate, with the appropriateness percentage of 100%. The inappropriateness of the prescriptions is nil in CKD 1 condition. Thus this study supports the hypothesis, which states that the prescription pattern of oral hypoglycemic agents in various nephropathy conditions is inappropriate.

Prescribed oral hypoglycemic agents which is highly responsible for hypoglycemic episodes are metformin +glimepiride (22.22%) (n=4), followed by voglibose (16.66%) (n=3), metformin (11.11%) (n=2), glimepiride (11.11%) (n=2).

The result of this study supports the previous studies carried out, which strongly implies that there is a need for dose adjustments of biguanides and sulphonylureas in case of CKD stage 3, and these class of drugs has to be avoided in CKD 4 & 5. For a good glycemic control, DM patients with CKD 4, ESRD have to be shifted to the newer class of OHA or insulin. So far in this study, the hypoglycemic episodes are highly found to be associated with sulphonylureas (mainly glimepiride), biguanides and voglibose. This emphasizes the safe use of the newer class of OHA for the optimal glycemic control in DM patients with CKD4, ESRD [21].

CONCLUSION

Biguanides and sulphonylureas (mainly glimepiride) still dominate the prescription pattern of DM-II, despite of the presence of the comorbidity such as nephropathy, which requires dose modifications and in a few cases avoidance of these class of OHA. These classes of drugs play a major role in causing neuroglycopenia and have to prescribed carefully with required dose modification in CKD stage 3, where as they have to be avoided totally in CKD stage 4 & CKD stage 5(ESRD).

Therefore there is a need for the reevaluation of the treatment regimen appropriate to the degree of kidney dysfunction. And the subjects need be monitored frequently for glycemic control and change in kidney function overtime preferably with the consultation of the concerned specialist. Newer classes of OHA are better tolerated and help in a good glycemic control when compared to biguanides and sulphonylureas. But the sufficient data is lacking to support the use of newer classes of OHA in nephropathy condition.

Therefore a more rigorous study, on a large scale must be carried out which highlights the inappropriate prescription of OHA in patients with kidney disease and minimize complications. This calls for creating more awareness among the primary care physicians and other clinicians involved in the care of diabetic patients.

ABBREVIATIONS: BUN: Blood Urea Nitrogen; SE.CR: Serum Creatinine; CUE: Complete Urine Examination; CKD: Chronic Kidney Disease; DM: Diabetes Mellitus; GFR: Glomerular Filteration Rate; CI: Confidence Interval; SGLT: Sodium Glucose Co Transporter 2; NH: New Hampshire; NKF: National Kidney Foundation; OHA: Oral Hypolycemic Agents; K/C/O: Known Case Of; M: Metformin; GM: Glimileride; ST: Sitagliptin; R: Repaglinide; V: Voglibose; P: Pioglitazone;Gc: Gliclazide; VL: Vildagliptin; OP: Out Patient; IP: In Patient; ESRD: End Stage Kidney Disease; G1: Grade 1; G2: Grade 2; G3a: Grade 3a Chronic Kisney Disease; G3b: Grade 3b Chronic Kidney Disease; G4: Grade 4 Chronic Kidney Disease; G5: Grade 5 Chronic Kidney Disease; GP: Glipizide; HBA1C: Glycosylated Haemoglobin.

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