Evaluation of Pattern of Use of Prescribed Oral Hypoglycaemic Drugs in Newly Diagnosed Diabetic Nephropathy Patients Visiting a Tertiary Care Hospital of Southern Bihar

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ABSTRACT

BACKGROUND

Diabetes is the most important risk factor for chronic kidney disease. Because of this, clearance of many oral hypoglycaemic drugs from our body is hampered and time of exposure to these drugs increases. Therefore, patients of diabetes need to be assessed frequently for the development of diabetic nephropathy and the dosage of oral hypoglycaemic drugs should also be modified accordingly. So, the purpose of this study was to evaluate the doses of prescribed OHAs in newly diagnosed diabetic nephropathy patients.

METHODS

A hospital based observational study was conducted at Narayan Medical College and Hospital, Sasaram, Bihar, India. A total of 600 diagnosed patients of diabetic nephropathy of age more than 18 years visiting for the 1st time in OPD of general medicine / nephrology department were included in the study after obtaining an informed consent. The results were expressed as a percentage of the assessed population.

RESULTS

Only about 38% of the total study population was taking doses of Oral Hypoglycaemic Agents (OHAs) according to their GFR status. 62% were taking wrong doses of OHAs with their respective renal function.

CONCLUSIONS

Treatment of diabetes in a CKD patient is more difficult than in non-CKD patient. GFR status should be monitored on regular basis in patients of diabetes with CKD. A significant number of these patients are still treated with wrong dosage of OHAs for their respective renal function.

KEYWORDS

Wrong Dose of OHA, Diabetic Nephropathy, Oral Hypoglycaemic Drugs

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BACKGROUND

Diabetes mellitus (DM) refers to a group of common metabolic disorders that share the common phenotype of hyperglycaemia.[1] It is one of the leading causes of chronic renal disease (diabetic nephropathy) and end stage renal disease (ESRD).[2] Chronic renal disease involves progressive decline in glomerular filtration rate with abnormal kidney function (as shown in Table 1).

Grade	Category	Range (mL / min / 1.73 m^2)
Grade 1	Normal or high	>90
Grade 2	Mildly decreased	60-89
Grade 3a	Mildly to moderately decreased	45-59
Grade 3b	Moderately to severely decreased	30-44
Grade 4	Severely decreased	15-29
Grade 5	Kidney failure	<15

Table 1. Kidney Disease Improving Global Outcome (KDIGO) Classification of Chronic Kidney Disease (Table Adapted from Harrison's Principles of Internal Medicine)[3]

Class and Medication	Dose Adjustment Based on eGFR
	Biguanide
Metformin	USA prescribing information: contraindication for men with serum creatinine ≥ 1.5 mg / dL and women with serum creatinine ≥ 1.4 mg / dL UK guideline allows metformin in patients with eGFR >30 mL / min / 1.73 m² KDIGO recommends metformin in patients with eGFR>45 mL / min / 1.73m²
	Sulfonylureas
Glimepiride	Initiate conservatively at 1 mg daily. Avoid use if eGFR<60 mL / min / 1.73m²
Glyburide or glibenclamide	Avoid use in patients with eGFR <60 mL / min / 1.73m².
	Meglitinides
Repaglinide	Initial dose of 0.5 mg before meals when eGFR <30 mL /min / 1.73 m².
Nateglinide	Caution when used with eGFR <30 mL / min / 1.73m². Initiate with 60 mg before meals.
	Thiazolidinediones
Pioglitazone	No dose adjustment required. Use with caution in patients with CKD and hypervolemia.
	GLP-1 receptor agonists
Exenatide	Avoid if eGFR<30 mL / min / 1.73m². When eGFR between 30 and 50 mL / min / 1.73m² dose should not exceed 5mcg
Lixisenatide	Avoid if eGFR<50 mL / min / 1.73m².
Liraglutide	Avoid if eGFR<60 mL / min / 1.73m².
DPP-4 inhibitors	Sitagliptin and saxagliptin dose adjustment required based on eGFR.
Sitagliptin	100 mg daily if eGFR <50 mL / min / 1.73m². 50 mg daily if eGFR 30-50 mL / min / 1.73m². 25 mg daily if eGFR <30 mL / min / 1.73m².
Saxagliptin	5 mg daily if eGFR <50 mL / min / 1.73m². 2.5 mg daily if eGFR <50 mL / min / 1.73m².
Linagliptin	No dose adjustment required
	SGLT-2 inhibitors
Canagliflozin	No dose adjustment required if eGFR<60 mL / min / 1.73m². 100 mg daily if eGFR 45 - 59 mL / min /1.73m².
Dapagliflozin	Avoid use if eGFR <60 mL / min / 1.73m², and discontinue use if eGFR <45 mL / min / 1.73m²

Table 2. Relationship among Therapeutic class, Medication Dose and Creatinine Clearance[6]

Chronic renal disease is associated with decreased clearance of many oral hypoglycaemic agents (OHAs) and their metabolites, prolonging the duration of exposure to the drug and its metabolites, more so in patients with moderate to severe renal disease.[4] Thus, a diagnosis of renal disease in patients with diabetes merits attention to the revision of the drug therapy of the patient. But, managing hyperglycaemia in CKD patients is difficult, partly due to the complexity involved in these patients, and partly due to less data supporting benefits of strict glycaemic control.[5] Many studies of antidiabetic drugs have excluded people with CKD. So, we lack solid evidence on the effectiveness and safety of these drugs.[6] It is also troublesome to manage these patients because of decreased GFR and its interference with the clearance and metabolism of antidiabetic agents and insulin resulting in difficult to predict hyperglycaemic peaks and hypoglycaemia.

As evident from the above table we can see that dose for almost every drug we use needs to be modified according to GFR status of patient. This can be done only through regular follow up and needs involvement of endocrinologist and nephrologist. But in current Indian scenario, small cities and rural area are still catered by general practitioners. Their ignorance regarding this can cause harm to the diabetic patients.

We wanted to study the pattern of use of prescribed oral hypoglycaemic drugs in diabetic nephropathy patients.

METHODS

This was a hospital based observational study done in Narayan Medical College and Hospital, located in southern Bihar. The study was done for a period of 6 months on OPD patients of diabetic nephropathy or known case, who visited for 1st time and fulfilled the inclusion criteria. Convenience sampling method was used.

Blood sugar (Fasting and PP), serum creatinine, Albumin-Creatinine Ratio (ACR) were determined. Ultrasonography was done.

The Cockcroft and Gault formula for estimating Creatinine Clearance: -

$$\mathbf{CrCl\ (mL\ /\ min)} = \frac{\mathbf{(140 - age) x\ Lean\ Body\ Weight\ (Kg)}}{\mathbf{Serum\ Creatinine\ (mg\ /\ dL)\ x\ 72} \times \mathbf{(0.85\ if\ female)}}$$

Diabetic nephropathy (CKD) will be established based on history, clinical examination, laboratory findings. Ultrasonography findings considered were reduced renal length, increased renal cortical echogenicity, reduced renal cortical thickness.

Inclusion Criteria

Patients of diabetes mellitus with chronic kidney disease who are-

1. above age of 18 years visiting 1st time in OPD
2. at or above stage 3b of Chronic Kidney Disease (KDIGO Classification) and deranged ACR, will be enrolled for the study after informed written consent.

Exclusion Criteria

1. Patients below age of 18 years
2. Diabetic patients with renal transplant

Prognosis of CKD by GFR and albuminuria categories: KDIGO 2012				Persistent albuminuria categories description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg / g <3 mg / mmol	30-300 mg / g 3-30 mg / mmol	>300 mg / g >30 mg / mmol
GFR categories (mL / min / 1.73m²) description and range	G1	Normal or high	≥ 90			
	G2	Mildly decreased	60 - 89			
	G3a	Mildly to moderately decreased	45 - 59			
	G3b	Moderately to severely decreased	30 - 44			
	G4	Severely decreased	15 - 29			
	G5	Kideney failure	< 15			

Figure 1. KDIGO Classification of CKD

In this study, no intervention or follow-up was done. The institutional ethical committee approved this study and there was no conflict of interest. Gradation of colour from green to red corresponds to increasing risk and progression of CKD, glomerular filtration rate.

RESULTS

Of 600 diabetic nephropathy patients, 300 were men and 300 were women. Only about 38% of the total study population was taking doses of Oral Hypoglycaemic Agents (OHAs) according to their GFR status. 62% (372 out of 600) were taking wrong doses of OHAs according to their respective CKD stage. Among males, 35% (105 out of 300) were taking modified doses whereas 65% (195 out of 300) were taking wrong doses of OHAs. Likewise, among females only 41% (123 out of 300) were taking modified doses while 59% (177 out of 300) were taking wrong doses. Table 4 shows the distribution of patients according to their GFR categories with 32.26% (120 out of 372) in stage 3b; 38.70% (108 out of 372) in stage 4 and 29.03% (108 out of 372) in stage 5.

Figure 2 shows different drugs, both monotherapy and combination therapy, that were used in wrong dosages among patients. In Monotherapy, Metformin was most commonly used in wrong dosage i.e. 22% (83 out of 372) of patients were taking wrong dosage of metformin. 15% (56 out of 372) were taking wrong dosage of glimepiride. In combination therapy, Glimepiride + Metformin (Dual drug therapy) was most commonly used by patients followed by combination of Metformin + Glimepiride + Pioglitazone (Triple drug therapy) i.e. 21% (77 out of 372) were on Dual Drug Therapy and 18% (68 out of 372) were on Triple Drug Therapy. 11% of patients were taking other OHAs in wrong dosages.

			Persistent Albuminuria		
			Normal to Mild increase	Moderate Increase	Severe Increase
GFR Categories (mL / min / 1.73 m²)			<30 mg / g	30-300 mg / g	>300 mg / g
G3b	Moderate to severely decreased	30-44	38	47	35
G4	Severely decreased	15-29	33	62	49
G5	Kidney failure	<15	29	34	45

Table 4. Patients Taking Wrong Doses of OHAs According to Their Renal Status

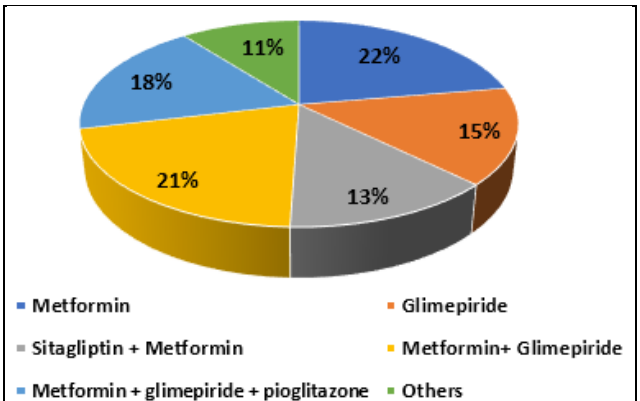

Figure 2. Different Drugs Used in Wrong Dosages

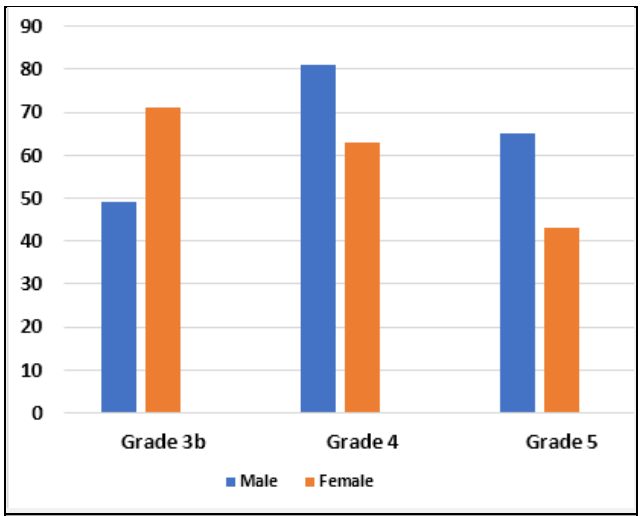

Figure 3. Number of Diabetic Nephropathy Patients on Wrong Dosages of OHA among Different Sex Groups

Figure 3 shows distribution of patients who were taking wrong doses of OHAs according to their renal stage among different sex group. In stage 3b, 49 males and 71 females were on wrong dosage of OHAs while in stage 4, Male patients were 81 and female patients were 63. In stage 5, 65 males and 43 females were on wrong doses of OHAs.

DISCUSSION

Chronic kidney disease and diiabetes mellitus coexist in more than one third of the patients. CKD patients who are on antidiabetic medications are at risk of developing drug induced hypoglycaemia. Thus, glycaemic control is essential in these patients and targets are HbA1c of 7 to 7.9% which also reduces cardiovascular risks.[8] As we can see, most of the patients of both sexes were taking wrong dosage of the drugs (62%) in our study. They were started on OHA or continued OHA's without considering their renal status.

Quantitative assessment of Urinary albumin to creatinine ratio and GFR should be done at least once in a year in diabetic patients.[9] Macroalbuminuria is said to be urinary ACR of >300 mg / g Creatinine and Microalbuminuria is defined as 30–300 mg albumin / day or 30–300 mg albumin / g creatinine (Cr) excreted in the urine.[10]

Many drugs having different mechanism of action and pharmacological profiles are being used in diabetic patients with the target of good glycemia control. But in patients of diabetes with chronic kidney disease, treatment option remains limited because of reduced glomerular filtration rate leading to accumulation of anti-diabetic drugs and their metabolites in the body leading to hypoglycaemic episodes and other side effects.[11] First line anti-diabetic drug like metformin can be used without any dose modification if patient's eGFR is > 60 mL / min / 1.73 m^2. If the eGFR is ≥ 45 – 59 mL / min / 1.73 m^2, metformin should be used cautiously with regular follow up every 3 months for renal status. If eGFR is ≥30 – 44 mL / min / 1.73 m^2, a 50% reduction in dose of metformin is done with maximum dose of 1000 mg per day. In our study metformin alone (22 %) and in combination with glimepiride, a sulphonyl urea (21%) was most commonly used in wrong dosage. And these two drugs are most commonly used semi urban and rural areas of Bihar. Glimepiride alone was used in 13% of total cases in wrong dosage. This probably explains the increase incidence of hypoglycaemia in renally compromised patients visiting our emergency. Route of excretion of sulfonylureas and their metabolites is renal dependent.[12] Drugs like Glyburide should be avoided with eGFR <60 mL / min / 1.73 $m.^2$ Glimepiride should be used in modified doses if eGFR is <60 mL / min / 1.73 m^2 and not to be used in patients with eGFR <30 mL / min / 1.73 $m.^2$ Thiazolidinediones like pioglitazone are metabolized in liver and do not cause hypoglycaemia. Therefore, they can be used in patients of renal disease. But due to their side effect of fluid retention, they are not safe in patients on dialysis.[12] Pioglitazones are rarely prescribed in our part by the local practitioners

Dipeptidyl peptidase 4 (DPP 4) inhibitors includes teneligliptin, sitagliptin, saxagliptin, linagliptin, and alogliptin. Most commonly used gliptin was Sitagliptin in combination with metformin. Around 13 % of the patients took these in wrong dose. Teneligliptin constituted a small portion in the others. Sitagliptin should be used in dose of 50 mg once daily with eGFR of ≥30 to <50 mL / min / 1.73 m^2 and in a dose of 25 mg once daily if eGFR is <30 mL / min / 1.73 m^2. Saxagliptin should be used in a dose of 2.5 mg daily if eGFR is ≤ 50 mL / min / 1.73 m^2. Linagliptin is safe in patients of diabetic nephropathy because only small amount of it is cleared through renal mechanism.[12]

SGLT2 inhibitors like Canagliflozin, Dapagliflozin, Empagliflozin and Ertugliflozin should not be initiated in patients if eGFR is persistently <45 mL / min / 1.73 m^2 and is contraindicated in eGFR of <30 mL / min / 1.73 m^2.[13]

Min Thinzar et al. in 2018 found that out of 9585 subjects, 85 were in severe CKD group and 21% of them were taking metformin. 20% of total subjects were taking inappropriately high dosing of DPP-4 inhibitors in CKD[14]. Muller. C et al. in 2016 in a cohort study of 301 consecutive adult type 2 diabetic patients found that 53.5% of patients were taking non-adjusted doses, mostly for metformin (30% of the whole cohort) and for sitagliptin (17.9% of whole cohort)[15]. Meyers J.L. et al. in 2015 in their study found that renal impairment is common but often undetected in type 2 diabetic patients. In these patients with renal impairment, Metformin and sitagliptin were frequently used at inappropriate doses.[16]

Because of all these problems, physicians need to frequently reassess the renal status of the patient and should modify the dose and drug of the patient to keep glycemia within normal value, to reduce the progression of disease, improving the quality of life and reducing comorbidities, especially to prevent hypoglycaemia, which is associated with increased cardiovascular risks.[6]

CONCLUSIONS

Diabetic nephropathy (CKD) is a common complication in T2DM. In these patients, use of Oral Hypoglycaemic Agents

is more complex than non-CKD patients. Tight glycaemic control is necessary in these patients to reduce the complications, but it should be done in a safe manner. Screening should be done in these patients on regular intervals for reductions in GFR or increase which indicates progression of nephropathy.[16] A good number of diabetic nephropathy patients are still treated with wrong dosage of OHAs for their respective renal function leading to more harm than benefit. As there is a dearth of endocrinologists and nephrologists in the rural belts like ours, bulk of the treatment is done by general practitioners who are ignorant about these facts. Also, there is paucity of data for moderate to severe disease. Therefore, a carefully performed clinical study in patients with moderate or severe renal disease is necessary to establish the way in which OHAs should be used in these patients and to share this knowledge for the benefit of patients.

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