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# Prescribing Trends of Antidiabetic Drugs in Type 2 Diabetes Mellitus Patients with Chronic Kidney Disease

Nafisa Akkas[1]* Md. Tanzilur Rahman[2] Riti Yusuf[3] Tripti Moni Saha[4]
Maurin Azad[5] Sumi Das[1] Taslima Akter[1]

## Abstract

**Background:** Patients suffering from Type 2 Diabetes Mellitus with chronic kidney disease is increasing in recent years. There is lack of studies on the prescribing trends of antidiabetic drugs in our country regarding Type 2 Diabetes Mellitus with chronic kidney disease patients. The aim of this study was to assess the prescribing trends of antidiabetic drugs in Type 2 Diabetes Mellitus with chronic kidney disease patients.

**Materials and methods:** A cross sectional study was performed from July 2022 to June 2023, by analyzing patients attending OPD of Endocrinology and Nephrology Department of SSMCMH and BIRDEM. Total 344 participants were enrolled after meeting the selection criteria.

**Results:** Mean age of the participants was 65.6 years with a male gender predominance (55.2%). Mean HbA1c was 7.40. Majority of the participants (39.5%) were in stage 3b. DPP-4 inhibitors were frequently prescribed as single drug (23.5%) and also SGLT2 inhibitors (16.0%). Among the combination therapy, insulin + DPP-4 inhibitor (28.8%) was used mostly prescribed followed by metformin + SGLT2 inhibitor (12.5%).

**Conclusion:** In our study the combination of metformin and SGLT 2 inhibitor were found to be used less frequently. Nonetheless, it is evident that its utilization was lesser in the previous year than it is currently. Thus, we can conclude that this medications have been used more frequently in recent years.

**Key words:** Chronic kidney disease; KDIGO guideline; Prescribing trends; Type 2 Diabetes Mellitus.

1. Lecturer of Pharmacology and Therapeutics
Chittagong Medical College, Chattogram.
2. Junior Consultant of Radiology and Imaging
250 Beded General Hospital, Noakhali.
3. Assistant Professor of Pharmacology and Therapeutics
Sir Salimullah Medical College, Dhaka.
4. Assistant Professor (cc) of Pharmacology and Therapeutics
Bikrampur Bhuiyan Medical College, Dhaka.
5. Assistant Professor (cc) of Pharmacology and Therapeutics
Zainul Haque Sikder Women's Medical College, Dhaka.

***Correspondence: Dr. Nafisa Akkas**
*Cell : 01725 01 55 16*
*E-mail: nafisaakkas1993@gmail.com*

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## Introduction

In present era, Diabetes Mellitus has become one of the most common non communicable diseases and also become one of the fastest growing global health emergencies of the 21st century. About 536.6 million people found to be suffering from Diabetes Mellitus globally.[1] Among them 90% of the patients were diagnosed as Type 2 Diabetes Mellitus.[2] In Bangladesh there is a dreadful rise in this disease's progression from 8.4 million in 2011 to 13.1 million by 2021. It is alarming that, Bangladesh is in the top 8th position among other countries of the world regarding this. People with uncontrolled Diabetes Mellitus have an increased risk of developing several life-threatening micro and macro vascular complications.[3] Poor glycemic control in Diabetes Mellitus can be prevented by using appropriate antidiabetic agents.[4,5] Stratton et al. observed that 1% reduction of mean $HbA_1c$ significantly reduces diabetes related deaths (21%) as well as microvascular complications (37%).[6]

Chronic kidney disease is the most common (Approximately 40%) microvascular complication of Type 2 Diabetes Mellitus resulting from hyperglycemia.[7,8,9] Diabetes Mellitus has become the leading cause of chronic kidney disease[10]. The prevalence is extremely high in Bangladesh too.[11,12] According to KDIGO, 2022, Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease, glycemic control is based on a combination of metformin and SGLT2 inhibitors (SGLT2i) for Type 2 Diabetes Mellitus with Chronic Kidney Disease (CKD) when eGFR is >30 ml/min/1.73m$^2$. SGLT2 inhibitors are recommended for patients with Type 2 Diabetes Mellitus and Chronic Kidney Disease (CKD) because SGLT2 inhibitors can reduce albuminuria dramatically by 30 to 40%.[13,14] Prescription trends monitoring study is a tool for assessing the prescribing, dispensing and distribution of medicines.[15] Several previous studies in Bangladesh have raised concerns about prescribing trends of antidiabetic drugs to people with renal impairment. Thus

irrational prescribing can lead to increase in cost of drug therapy, which may lead to non-adherence.[16] The aims of this study was to assess the prescribing trends of antidiabetic drugs in Type 2 Diabetes Mellitus with chronic kidney disease patients.

## Materials and methods

A descriptive, observational and cross-sectional study was performed from July 2022 to June 2023, by analyzing participants followed up by one physician in the Endocrinology and Nephrology Department of Sir Salimullah Medical College Mitford Hospital and BIRDEM, Dhaka, Bangladesh. 344 participants diagnosed as Type 2 Diabetes Mellitus with chronic kidney disease were included for this study. At first ethical clearance and permission were taken from the Institutional ethical committee of Sir Salimullah Medical College Mitford Hospital, Dhaka.The following variables were sought: age, gender, stages of chronic kidney disease, Duration of Type 2 Diabetes Mellitusetc were collected according to participant's history. HbA1c, eGFR, serum creatinine, $HbA_1c$, were sought from the participant's previous laboratory investigation reports. Antidiabetic drugs are analyzed by observing the prescriptions. Statistical analysis was performed using SPSS (Version 23.0). Qualitative variables (Sex, co morbidities) of this study was expressed as percentage. Quantitative variable (e.g age) was expressed as mean ± standard deviation.

## Results

Our study shows mean age was 65.6 with male gender predominance. Most of the participants were from lower socioeconomic class (47.1%) (Table I)

**Table I** Distribution of demographic characteristics of the study participants (n=344)

| Variables | Number of participants | Percentage (%) |
|---|---|---|
| Age (Years) | | |
| 40-49 | 21 | 6.1 |
| 50-59 | 114 | 33.1 |
| 60-69 | 164 | 47.7 |
| 70-79 | 44 | 12.8 |
| 80 | 1 | 0.3 |
| Mean ±SD | 65.6±7.7 | |
| Range (Min-max) | 40.0-80.0 | |
| Gender | | |
| Male | 190 | 55.2 |
| Female | 154 | 44.8 |
| Socioeconomic status | | |
| Lower | 162 | 47.1 |
| Middle | 124 | 36.1 |
| Upper | 58 | 16.9 |

**Table II** Distribution of clinical characteristics of study participants

| Clinical characteristics | Number of participants | Percentage (%) |
|---|---|---|
| $HbA_1C$ (%) | | |
| <6.5 | 170 | 49.4 |
| >6.5 | 174 | 50.6 |
| Mean±SD | 6.39±1.29 | |
| Fasting plasma glucose (mmol/L) | | |
| <7.0 | 149 | 43.3 |
| ≥7.0 | 195 | 56.7 |
| Mean±SD | 8.18±2.48 | |

This study shows that 50.6 participants have uncontrolled HbA1c >6.5% and 56.7% participants have fasting blood glucose level >7.0 mmol/L (Table II)

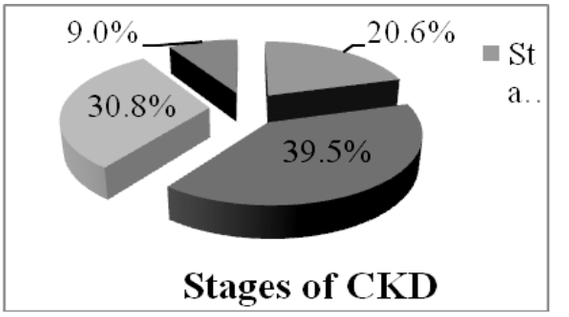


**Figure 1** Prevalence of CKD by stage 3a-5

Our study shows 39.5% participants were in stage 3b chronic kidney disease (Figure-1).

**Table III** Trends of using antidiabetic drugs in different stages of CKD(n=344)

| Antidiabetic drugs | Stages of CKD | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Stage 3a (n=71) | | Stage 3b (n=136) | | Stage 4 (n=106) | | Stage 5 (n=31) | |
| | n | % | n | % | n | % | n | % |
| **Single class** | | | | | | | | |
| DPP-4 inhibitor (23.5%) | 21 | 29.6 | 17 | 12.5 | 43 | 40.6 | 0 | 0.0 |
| SGLT2 inhibitor (16.0%) | 19 | 26.8 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| Insulin (6.10%) | 14 | 19.7 | 41 | 30.1 | 0 | 0.0 | 0 | 0.0 |
| Metformin (5.5%) | 1 | 1.4 | 0 | 0.0 | 5 | 4.7 | 15 | 48.4 |
| Sulfonylurea (0.0) | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| **Combination classes** | | | | | | | | |
| Insulin + DPP-4 inhibitor (28.8%) | 8 | 11.3 | 18 | 13.2 | 57 | 53.8 | 16 | 51.6 |
| Metformin + SGLT2 inhibitor (12.5%) | 2 | 2.8 | 41 | 30.1 | 0 | 0.0 | 0 | 0.0 |
| DPP- 4inhibitor + SGLT2 inhibitor (2.0%) | 3 | 4.2 | 4 | 2.9 | 0 | 0.0 | 0 | 0.0 |
| Metformin + Sulfonylurea (3.5%) | 12 | 16.9 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| Insulin + SGLT2 inhibitor (5.2%) | 4 | 5.6 | 13 | 9.6 | 1 | 0.9 | 0 | 0.0 |

Abbreviations: DPP-4 inhibitor- Dipeptidyl peptidase-4, SGLT2 inhibitor- Sodium Glucose Co Transporter 2 inhibitors

On evaluation of individual Anti Diabetic drugs prescribed, it was found that DPP-4 inhibitor (23.5%) was the most commonly prescribed mono therapy followed by SGLT2 inhibitor (16.0%). Whereas Insulin and DPP-4 inhibitor (28.8%) followed by Metformin and SGLT2 inhibitor (12.5%) were the most commonly prescribed dual anti diabetic drug combinations (Table III)

**Discussion**

Diabetes Mellitus has become one of the major health issue as the number of patients suffering from it's complications are increasing day by day. In Bangladesh currently the prevalence of Diabetes Mellitus with CKD patients is 34% and it is alarming that this number is increasing very rapidly.[12] Rigorous blood glucose control reduces the rate and progression of microalbuminuria. Many new renoprotective antidiabetic drug therapies are available in current guideline. So this study was carried out with an aim to assess the prescribing trends of antidiabetic drugs in Type 2 Diabetes Mellitus with CKD patients.

In our study, the range of age of study participants was 40-80 years and majority was from 61-70 years (42.7%). The mean age was 65.6 years which was similar to otherprevious studies.[17,18] However this finding did not match with another study where mean age was found 74 years.[19] This dissimilarity may happen due to geographical differences.

This study showed slightly male predominance among the participants. It was observed that 55.2% (190) participants were male and 44.8% (154) participants were female. This data coincides with other studies[19, 20]. Socioeconomic status is very important for selecting drug options. Most of the participants in this present study belonged to lower socioeconomic class (47.1%). These findings are comparable with Tanvir et al.[21]

Staging of CKD is very important for treatment purpose and drug choice. In this study about 39.5% (136) participants were in stage 3b, 30.8% (106) participants were in stage 4 and 20.6% (71) participants were in stage 3a. 9% (31) had end stage renal disease (ESRD) (Stage 5). This findings was in concurrence with the result of Abreu et al.[19] However in the result of Al-Ramahi et al. the ESRD (Stage 5) patients were as high as 90%.[21] The reason for this difference lies in the inclusion criteria of the study. In our study, the participants were selected from OPD but in Al-Ramahi et al. study participants were selected from In Patients Department (IPD).[21]

In our observational study mean $HbA_1c$ was 7.40%. Suchlike findings also observed by a study reported by Manski-Nankervis et al.[22] In their study they found an average $HbA_1c$ 7.3%.We also observed that mean eGFR was 33.03.

According to this observational study, it is observed that among all the antidiabetic regimens, 12.5% (43/344) of Diabetes patients received the combination of an SGLT2 inhibitor with metformin, in contrast to 28.8% (99/344) of DPP-4 inhibitor with insulin. None of the participants prescribed with GLP-1RA, thiazolidinediones, $\alpha$ glucosidase inhibitors.This could be due to the fact that these drugs are not recommended in DM with CKD patients except GLP-1RA. GLP-1RA is recommended but it is too expensive and most of participants of our study were poor. This findings was comparable with other study where they observed DPP-4 inhibitors was most commonly prescribed drug (56.4%), followed by insulin (34.6%), biguanides (32.7%) SGLT-2 inhibitors (22.6%), sulfonylureas (11.6%), GLP-1 agonists (3.4%), $\alpha$ -glucosidase inhibitors (1.5%) and thiazolidinediones (0.7%).[19] Nevertheless according to an Australian study, biguanides(81%) were most prescribed drug followed by sulfonylureas (52%) and DPP-4 inhibitor (38%).[22]

KDIGO, 2022, Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease recommended an SGLT2 inhibitor in combination with metformin as first line treatment in Type 2 Diabetes Mellitus with CKD patients.[13] A study conducted by Saibal et al. in Bangladesh found that only 1.1% SGLT2 inhibitors were prescribed in their studies.[23] In our study we found this number is increasing significantly. Metformin with SGLT2 inhibitor was less frequently prescribed may be due to low eGFR and high price. Majority of the participants had serum creatinine above 1.5 mg/dl and FDA does not recommend to use metformin with serum creatinine above 1.5 mg/dl.[24] So we got less participants with metformin.In this study, most of the participants were treated with DPP-4 inhibitor with insulin where majority of the participants

were older with lower eGFR and higher $HbA_1C$. Only linagliptin is prescribed among all the other DPP-4 inhibitors.This may be due to linagliptin is safer for aged and renal impaired patients because no dose adjustment is required as linagliptin is biliary excreted.[17] Insulin was more frequently prescribed to participants with uncontrolled glycemic control and also for limited medication choices among Diabetes patients with lower eGFR. Sulfonylureas was not used alone as a mono therapy but used in combination with metformin in 3.5% participants. This may be due to increase chance of hypoglycemia with sulfonylureas in patients with impaired renal function. Besides these drugs, insulin + SGLT2 inhibitor 18 (5.2%) DPP-4 inhibitor+ SGLT2 inhibitor 7 (2.0%) metformin + DPP-4 inhibitor 4 (1.2%) and metformin + insulin 1 (0.3%) combinations also prescribed.

**Limitations**

This study was carried out with a small size over a short period of time. Also limited participants only from two institutions.

**Conclusion**

In the recognized KDIGO guideline, the combination of metformin and SGLT2 inhibitor is recommended as first line drug. In our study we've found that this combination is not being used that much. However it can be seen that in the previous years, its usage have been lower than what it is now. So we can say that the prescribing of this combination of drugs has been increased in recent years.

**Recommendations**

Further study can be done in other tertiary level hospitals in Bangladesh to find out the variations in the treatment. Physicians should use antidiabetic regimens according to current guideline. Further follow up study should be done on the participants receiving metformin and SGLT2 inhibitor combinations.

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**Contribution of authors**

NF-Conception, design, acquisition of data, data analysis, data interpretation, drafting & final approval.

TR-Manuscript drafting &critical revision of content.

RY- Data analysis, drafting & final approval.

TMS-Interpretation of data, drafting & final approval.

MA-Data analysis, critical revision & final approval.

SD-Acquisition of data, interpretation of data, drafting & final approval.

TA-Acquisition of data, interpretation of data, drafting & final approval.

**Disclosure**

All the authors declared no conflict of interest.

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