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Research Article

Drug Interactions of Antidiabetic drug

Identifying Drug-Drug Interactions in Diabetic Patients with Chronic Kidney Disease: Pharmacist's Interventions

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Abstract: Drug-drug interactions (DDIs) can negatively affect patients 'therapeutic outcomes. Therefore, our aim was to evaluate DDIs among diabetic patients with chronic kidney disease (CKD). To achieve this aim, our objectives were to identify DDIs in diabetic patients with CKD admitted to the Medicine Department of the tertiary care hospital and to evaluate pharmacist's interventions in managing DDIs among these patients. A prospective observational study was conducted over 6 months. The pharmacist performed a medication chart review, and DDIs were identified by using Lexicomp® drug interaction. The pharmacist informed prescribers regarding the occurrence of DDIs, and all pharmacist`s interventions were classified according to Pharmaceutical Care Network Europe. Overall 307 DDIs were identified among a total of 119 study patients with an average of 2.6 DDIs per patient. The most of identified DDIs (205, 66.7%) belonged to the interaction risk-rating category of C, which indicates that DDIs required close monitoring of patients' therapy to avoid any potential adverse outcome. DDIs that needed to be managed by considering therapy modification (risk-rating category of D) and avoiding drug combination (risk-rating category of X) were accounted for 19.2% and 14.0% of all detected interactions, respectively. Interactions between Furosemide–Insulin (43, 14.0%), Amlodipine–Calcium carbonate/vitamin D3 (35, 11.4%) were found to be among most commonly identified DDIs. The pharmacist delivered different types of interventions to prescribers, which ranged from monitoring of therapy outcome to stopping DDIs. A great proportion of delivered pharmacist's interventions (87%) were accepted by prescribers. Clinically significant DDIs occurred commonly in hospitalized diabetic patients with CKD. The pharmacist delivered important interventions in timely identifying DDIs.

Keywords: Drug-Drug Interaction, Diabetes Mellitus, Chronic Kidney Disease and Pharmacist's Intervention

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1. INTRODUCTION

Diabetes Mellitus (DM) is a multi-factorial chronic health condition triggered by several genetic and/or environmental factors. [1, 2] Type 2 DM (T2DM), one of the most common metabolic disorders, is caused by a combination of two primary factors: defective insulin secretion by pancreatic β - cells and the inability of insulin-sensitive tissues to respond appropriately to insulin. Because insulin release and activity are essential processes for glucose homeostasis, the molecular mechanisms involved in the synthesis and release of insulin, as well as in its detection are tightly regulated. Defects in any of the mechanisms involved in these processes can lead to a metabolic imbalance responsible for the development of the disease. [3] The World Health Organization (WHO) Global report on diabetes shows that the number of adults living with diabetes has almost quadrupled since 1980 to 422 million adults and is expected to increase to 693 million by 2045. [4] T2DM can cause long-term microvascular and macrovascular complications, contributing to the increased morbidity and mortality among these patients. Diabetes is a major risk factor for cardiovascular disease (CVD) and is a leading cause of chronic kidney disease (CKD). Diabetes-related nephropathy (also known as diabetic nephropathy1 or diabetic kidney disease [DKD]) develops in approximately 40% of patients with T2DM. [5] Kidney disease in patients with diabetes can be a result of microvascular complications from diabetes, a concomitant kidney disease of other origin or a combination of the two. [6] CKD is a progressive loss of renal function that occurs over a period of months or years and can affect people at any ages of any races. CKD is a global health concern. Approximately 1 out of 10 people in the world's population have some degree of CKD. However, the risk of CKD is higher among African Americans, Hispanics, American Indians, and people of South Asian origin, which can be due to a higher rate of diabetes and hypertension among these populations. CKD is associated with a high rate of morbidity, healthcare expenditures, and mortality. [7] Diabetic patients with CKD are prescribed multiple medications (polypharmacy) due to either slowing deterioration of kidney function or managing comorbidities, such as DM, hypertension, cardiovascular diseases, and anemia. [8] The presence of comorbidities and associated polypharmacy have major implications on patients' ability to cope with treatment. [9] The need for complex drug regimens in diabetic patients with CKD potentiates the risk of occurrence of medication-related problems, such as drug–drug interactions (DDIs), [10] and the risk increases as CKD progresses. [11] In addition, the influence of CKD on the pharmacokinetic and pharmacodynamic mechanism of medications increases the risk of the occurrence of DDIs-related adverse outcome in this cohort. [12-13] Pharmacist`s interventions have been demonstrated to alleviate medication-related problems, including DDIs, and contribute to improving medication usage and management of comorbidity in diabetic patients with CKD. [14-15] Moreover, involvement of pharmacist has a beneficial role in adjusting medication dose regimens of patients with CKD admitted in a hospital setting, where patients are more vulnerable to medication-related complications. [16-17]. Given the complexity of medication regimens for diabetic patients with CKD, existing comorbidities, alteration of pharmacokinetic, and pharmacodynamic of medications prescribed for these patients, there is the requirement to identify DDIs in diabetic patients with CKD performed by pharmacist to establish enhanced pharmacy services among these vulnerable patients. In addition, the intervention of pharmacist with healthcare team for identifying and managing DDIs, and improving therapeutic outcomes in diabetic patients with CKD is crucial for continued drug safety monitoring. [18] Therefore, this study aimed to identify common DDIs in diabetic patients with CKD admitted in the Medicine Department of hospital and to evaluate pharmacist's interventions in managing DDIs among these patients.

2. MATERIALS AND METHODS

2.1 Study Design, Setting and Participants

A prospective observational study was conducted in the Medicine Department of the Jayanagar General Hospital, a tertiary care academic hospital located in Bangalore. The study was performed over a period of 6 months. Diabetic patients with CKD admitted to the Medicine Department of this hospital are treated by a multidisciplinary team, mainly composed of physicians, nephrologists, senior and junior residents, nurses, and pharmacist. Pharmacists are involved in the monitoring of pharmacotherapeutic regimens of patients, attending medical rounds, and answering drug queries. Moreover, dedicated pharmacist at the study site has a proactive participation with healthcare team in drug therapy review, medication reconciliation, and screening for DDIs of hospitalized patients. During the working hours of the pharmacist prospectively reviewed patients' medication charts to assess the appropriateness of prescribed medications.

2.2 Inclusion Criteria

Patients (age ≥18 years) admitted to the Medicine Department and diagnosed with type 2 DM and CKD were included in this study. Informed consent was obtained from patients or the patient's caregiver whenever the patient was not able to communicate. The study received approval from the Institutional Human Ethics Committee of Nargund College of Pharmacy, Bangalore, India (Reference number: NAG/IEC/2021-19).

2.3 Exclusion Criteria

Patients with type 1 and gestational diabetes were not included. Diabetic patients with CKD who stayed less than 24 hours in the Medicine Department, discharged against medical advice or discharged on patient`s request were excluded. Also, patients who were unable to give consent were excluded.

2.4 Data Collection and Identifying DDIs

The dedicated pharmacist reviewed patients' medication charts and documented prescribed medications during working hours (Monday to Saturday, 09:00–16:00). The process of medication chart review was performed twice daily (after morning and afternoon medical rounds) to avoid miss out of newly added medication, STAT, and Si Opus Sit (S.O.S, if necessary) medication orders. In addition, demographic information of patients and relevant medical history including main complaints, history of present illness, and past medical/medication history were collected by the clinical pharmacist. The glomerular filtration rate was estimated by using the modification of diet in the renal disease equation. [19] CKD definition and categorization of CKD stages were according to the Kidney Disease Outcomes Quality Initiative.

[20] DDIs were identified and categorized by using Lexicomp® drug interaction. According to Lexicomp® drug interaction, DDIs with a risk-rating category of "C" (drug interaction required monitoring to detect potential adverse outcome), "D" (drug interaction has a high risk of the occurrence of adverse outcome, and safer alternative treatment should be considered), and "X" (drug combination is contraindicated and must be avoided) are clinically significant. Lexicomp® DDIs with the risk-rating categories of A and B (no action is required to manage drug interaction) do not imply the clinically significant impact on the patient's outcome of therapy. Therefore, we only considered DDIs with the risk-rating categories of C, D, and X (clinically significant DDIs), which require particular intervention and management.

2.5 Pharmacist's Interventions

The pharmacist participated in daily multidisciplinary medical rounds, delivered proposed recommendations to prescribers, and intervened in managing identified DDIs. The pharmacist's interventions were classified according to the Pharmaceutical Care Network Europe version 8.02. [21] The study outcomes were numbers and types of pharmacist's interventions in managing encountered DDIs. The type of these interventions was based on the risk-rating categories of identified DDIs and recommendations provided by Lexicomp® drug interaction. For the risk-rating category of C (monitor therapy), the pharmacist recommended monitoring patients' clinical outcomes, such as blood pressure, heart rate, blood glucose, serum electrolytes, and serum creatinine more frequently or more closely. For example, the interaction between furosemide and insulin may diminish the therapeutic effect of insulin. Hence, for managing this interaction, the patient's blood glucose required more frequent monitoring to ensure appropriate glycemic control. On the contrary, for DDIs with the risk-rating categories of D and X, the pharmacist recommended considering therapy modification and avoiding the combination, respectively. For example, to avoid the occurrence of severe hypotension, the pharmacist recommended stopping the combination of nitroglycerine and sildenafil.

3. STATISTICAL ANALYSIS

Collected data of study patients were entered into a Microsoft Excel spreadsheet during the study period. Descriptive statistics were applied for calculation of variables such as mean, standard deviation, frequencies, and percentages of patient`s demographic/clinical characteristics, CKD stages, pharmacist's interventions, identified DDIs, and DDIs-related risk and severity rating. The independent variables like age, gender, the length of hospital stay, the number of prescribed medications, and the number prescriber involved and the number of DDIs were also analyzed. The Statistical Package for Social Sciences for Windows, version 22.0 was applied to study data analysis.

4. RESULTS

During study period, a total of 119 patients met the study criteria and were included in to the study. The mean age of 63.2 ± 9.7 years was calculated for study patients of whom 73 (61.3%) patients were male. The mean length (days) of hospital stay and the mean number of prescribed medications were 15.1 ± 4.6 and 19.4 ± 7.1, respectively. Approximately half of the patients (51, 42.9%) were in stage 5 of CKD (Table 1).

Table 1: Demographic and clinical characteristics of study patients (N = 119)

Age (years)	
Mean ± SD	63.2 ± 9.7
Sex, n (%)	
Male	73 (61.3)
Female	46 (38.7)
Length of hospital stay (days)	
Mean ± SD	15.1 ± 4.6
Number of prescribed medications	
Mean ± SD	19.4 ± 7.1
Number of prescribed therapeutic classes	
Mean ± SD	10 ± 11.6
Number of specialized prescribers involved	
Mean ± SD	7 ± 5
Number of comorbidities	
Mean ± SD	3.5 ± 1.9
Alcohol intake, n (%)	
Yes	54 (45.4)
Smoking, n (%)	
Yes	58 (48.8)
CKD stage, n (%)	
3	19 (16.0)
4	46 (38.7)
5	51 (42.9)

SD, standard deviation; CKD, chronic kidney disease.

We evaluated different types of comorbidities among study patients. Hypertension (67, 22.4%), electrolyte imbalance (53, 17.7%), anemia (42, 14.1%), urinary tract infection (33, 11.0%), and ischemic heart disease (21, 7.0%) were found to be the most frequent comorbidities among patients (Table 2).

Table 2: Frequency of comorbidities in study patients	
Comorbidities	**N (%)**
Hypertension	67 (22.4)
Electrolyte imbalance	53 (17.7)
Anemia	42 (14.1)
Urinary tract infection	33 (11.0)
Ischemic heart disease	21 (7.0)
Cardiac failure	15 (5.1)
Sepsis	15 (5.1)
COPD	15 (5.1)
Bone mineral disease	13 (4.4)
CVA	9 (3.0)
Pulmonary thromboembolism	8 (2.9)
Pneumonia	8 (2.9)

COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident.

The dedicated pharmacist reviewed patients' medication charts to identify DDIs. The pharmacist identified a total of 307 DDIs, giving an average of 2.6 DDIs per patient. The most of identified DDIs (205, 66.7%) belonged to the interaction risk-rating category of C, which indicates that DDIs required close monitoring of patients' therapy to avoid any potential adverse outcome. Fifty-nine (19.2%) and 43 (14.0%) of identified DDIs were classified in the interaction risk-rating categories of D and X, which needed to consider therapy modification and stop drug combinations, respectively, to prevent the occurrence of adverse outcome (Table 3).

Table 3: Identified drug–drug interactions in study patients (N = 307)				
Drug-Drug Interaction	**N (%)**	**Potential Consequence**	**Interaction Risk Rating**	**Interaction Severity Rating**
Furosemide–Insulin	43 (14.0)	Diminishing therapeutic effect of insulin.	C, Monitor therapy	Moderate
Amlodipine–Calcium carbonate/vitamin D3	35 (11.4)	Diminishing therapeutic effect of amlodipine.	C, Monitor therapy	Moderate
Linezolid–Insulin	30 (9.8)	Enhancing hypoglycemic effect of insulin.	C, Monitor therapy	Moderate
Amlodipine–Calcium gluconate	25 (8.1)	Diminishing therapeutic effect of amlodipine.	C, Monitor therapy	Moderate
Nitroglycerine–Sildenafil	23 (7.5)	Enhancing vasodilatory effect of NTG.	X, Avoid combination	Major
Metoprolol–Clonidine	23 (7.5)	Enhancing AV-blocking effect of metoprolol. Enhanced rebound hypertensive effect of clonidine.	D, Consider therapy modification	Moderate
Atenolol–Clonidine	22 (7.1)	Enhancing AV-blocking effect of atenolol. Enhanced rebound hypertensive effect of clonidine.	D, Consider therapy modification	Moderate
Salbutamol–Metoprolol	21 (6.8)	Diminishing bronchodilatory effect of salbutamol.	C, Monitor therapy	Moderate
Tolvaptan–Sodium chloride (3%)	20 (6.5)	Enhancing adverse/toxic effect of tolvaptan.	X, Avoid combination	Major
Furosemide–Salbutamol	20 (6.5)	Enhancing hypokalemic effect of furosemide.	C, Monitor therapy	Moderate
Levofloxacin–Insulin	19 (6.2)	Enhancing hypoglycemic effect of insulin or can diminish therapeutic effect of insulin.	C, Monitor therapy	Moderate
Digoxin–Amiodarone	14 (4.6)	Increasing serum concentration of digoxin.	D, Consider therapy modification	Major
Furosemide–Amikacin	12 (3.9)	Enhancing adverse/toxic effect of amikacin.	C, Monitor therapy	Moderate

NTG, nitroglycerine; AV, atrioventricular.

The pharmacist informed prescribers about identified DDIs. Most of pharmacist's interventions at the prescriber level were interventions which were proposed to concerned prescribers (261, 85.0%). Analysis of pharmacist's interventions at the drug level

showed that the dosage changed (71, 23.1%) and drug stopped (61, 19.9%) were among most frequent types of provided interventions. A great proportion of these interventions (267, 87.0%) was accepted and fully implemented by the prescribers (Table 4).

Table 4: Pharmacist's interventions in managing identified drug–drug interactions

Pharmacist's intervention	N (%)
At prescriber level	
Prescriber informed only	47 (15.3)
Prescriber asked for information	123 (40.1)
Intervention proposed to prescriber	261 (85.0)
Intervention discussed with prescriber	193 (62.9)
At drug level	
Drug changed	34 (11.1)
Dosage changed	71 (23.1)
Formulation changed	19 (6.2)
Instructions for use changed	37 (12.1)
Drug stopped	61 (19.9)
Other intervention (outcome monitored)	
Blood glucose monitored more frequently	59 (19.2)
Blood pressure monitored more closely	37 (12.1)
Serum electrolytes monitored more frequently	51 (16.6)
Heart rate monitored more closely	33 (10.8)
Serum creatinine monitored more frequently	19 (6.2)
Acceptance of the intervention by prescriber	
Intervention accepted and fully implemented	267 (87.0)
Intervention accepted, partially implemented	25 (8.1)
Intervention accepted but not implemented	15 (4.9)

5. DISCUSSION

The current study aimed to identify common DDIs in diabetic patients with CKD admitted in the Medicine Department of hospital and also to evaluate pharmacist's interventions in managing DDIs among these patients. Our analysis showed that 307 DDIs with an average of 2.6 interactions per patient occurred, which required pharmacist's intervention to inform concerned prescribers. This finding indicates that DDIs occur commonly among diabetic patients with CKD admitted in the hospital. The common occurrence of DDIs in hospitalized diabetic patients with CKD can be due to several potential reasons. We identified an average number of 19.4 medications prescribed per study patient. Also, our analysis showed 299 numbers of comorbidities. Prescribing of multiple medications (polypharmacy) and the presence of comorbidities are found to be associated to occurrence of MRPs such as DDIs in patients diagnosed with CKD. [10, 22-23] These patients are prescribed more complex pharmacotherapeutic regimens to slow down the progression of their chronic disease, and to manage associated comorbidities as well. Hence, as the number and the severity of these comorbidities advance, the number of prescribed medications increases, in turn, the risk of DDIs is higher. [8] A study conducted by Hiroshi Kimura, et al. with the aim to explore the association between polypharmacy with kidney disease progression in adults with CKD concluded that the use of a high number of medications (polypharmacy) was associated with a high risk of kidney failure, cardiovascular events, and all-cause mortality among hospitalized patients. [24] Another study performed by Elena-Codruț a Dobrică, et al. with the aim to evaluate the use of polypharmacy in type 2 diabetes mellitus vs. non-diabetes patients. Authors emphasized that polypharmacy should be considered as an area of serious concern in patients with type 2 diabetes mellitus. Data showed that these patients received more number of drugs than non-diabetes counterparts and consequently were exposed to more DDIs. [25] Therefore, higher number of prescribed medications among diabetic patients with CKD can be associated with both greater chance for occurrence of DDIs and further related comorbidities. Our drug interactions analysis showed that most common identified DDIs were interaction between furosemide– insulin and amlodipine–calcium carbonate/vitamin D3. Medications involved in such DDIs are an example of interactions that occurred between medications prescribed for the management of diabetes mellitus- and CKD-related symptoms, such as hyperglycemia, and volume overload, which are well-known symptoms of diabetes-related comorbidities. [7] Furosemide may diminish the therapeutic effect of insulin, resulting in hyperglycemia or loss of diabetic control, and necessitate dose escalation of the antidiabetic agent. Therefore, patients are in need of monitoring blood glucose more frequently. [26] In addition, interaction between amlodipine and calcium carbonate may diminish the therapeutic effect of calcium channel blockers. It is presumed that increasing the extracellular calcium concentration may oppose the effects of the calcium channel blocker. Therefore, patients should be monitored for decreased therapeutic effects of calcium channel blockers if a calcium supplement is initiated/dose increased, or increased effects if a calcium supplement is discontinued/dose decreased[27]. Twenty-three (7.5%) DDIs (contraindicated interaction) occurred due to the prescription of nitroglycerine and sildenafil for the management of cardiovascular-related comorbidities. It is, therefore, reasonable to consider prescribed medication for the management of comorbidity as a contributing factor in the

occurrence of DDIs in hospitalized diabetic patients with CKD. Additionally, our findings showed that approximately half of study patients (51, 42.9%) were in stage 5 of CKD. As the stage of CKD advances, the number of prescribed medication increases, thereby the risk of DDIs will increase consequently. [28-29] Thus, while managing diabetic patients with CKD, especially when patients are at the advanced stage of CKD, it is imperative to consider the stage of CKD as another contributing factor for the occurrence of DDIs. [10] Overall, we identified 307 DDIs among study patients. The dedicated pharmacist informed and provided interactions risk and severity ratings to concerned prescribers. The majority of interventions with prescribers were performed during medical rounds by proposing DDIs management to prescribers, which indicates the collaboration of the pharmacist with the healthcare team in the delivery of drug therapy management. This activity of pharmacists can improve their recognition among healthcare providers, increase the visibility of pharmacists in the healthcare team, and consequently gain a higher acceptance rate by prescribers. [30-31] A great proportion of these interventions (267, 87.0%) was accepted and fully implemented by the prescribers which indicate pharmacists as an invaluable source of drug knowledge [32] who can have a medication-related information role in identifying and management of DDIs in diabetic patients with CKD. With the increasing complexity of therapy regimens and overwhelming numbers of patients with type 2 diabetes, the pharmacist's role has expanded beyond dispensing medications, and monitoring for therapeutic regimens to evaluate patient outcomes. [33] Pharmacists' interventions as part of the patient's healthcare team can improve diabetes therapeutic outcomes, substantiating the important role of pharmacists in team-based diabetes management[34]. The type of provide interventions depended on identified DDIs risk-rating categories. The most frequent type of provided interventions was found to be monitoring the patient's therapy outcome (199, 64.8%) to manage the most common identified DDIs category (category C, monitor therapy). Interventions such as the change of dosage, formulation, and instructions for drug use were delivered for the management of DDIs with the risk-rating category of D. The order for immediate discontinuation of drugs was the type of intervention mostly provided for the management of contraindicated DDIs (risk-rating category of X). These interventions were provided at the prescriber level which emphasized the necessity for a clear and thorough collaboration of the pharmacist in identifying, monitoring, and managing pharmacotherapeutic regimens of diabetic patients with CKD. A systematic review stated a wide range of implemented interventions by pharmacists in pharmacotherapeutic care of patients with CKD. These interventions include modifying drug doses, recommending new pharmacotherapy, interacting with the multidisciplinary team, requesting and monitoring laboratory parameters, and assessing the appropriateness of prescribed medications for identifying MRPs, such as DDIs. Our types of provided interventions during study period are largely in line with the report of this review study. [35] Our study has several limitations. Due to the unavailability of documented data before this study, we could not evaluate the impact of the pharmacists' interventions on reducing clinical outcomes, such as length of hospital stay, the number of hospital readmission, or financial savings. This study was conducted in one medicine department of a tertiary care hospital, and our findings may not be generalized. We did not detect patient harm associated with identified DDIs. Also, we did not evaluate the long-term impact of the pharmacist's interventions on patient outcomes. The long-term impact of the pharmacist's interventions on the improvement of clinical outcomes of diabetic patients with CKD admitted to the medicine department can be an area for future research.

6. CONCLUSION

The current study revealed a common occurrence of clinically significant DDIs in diabetic patients with CKD admitted to the medicine department of the hospital. The pharmacist's intervention played an important role in identifying and informing prescribers about the occurrence of DDIs among these patients. The delivered interventions by the pharmacist were well-accepted by prescribers, and the continuation of pharmacy services in the study setting may further improve the appropriate selection of medications and patient safety.

7. AUTHORS CONTRIBUTION STATEMENT

Armita Sabahi and Namitha K.B developed the study theory, objectives, and methodology design. Armita Sabahi performed a major contribution to the acquisition of patient-related data, and data analysis. Namitha K.B supervised the study process and also supported in data analysis. All authors discussed the results and contributed to the writing of the manuscript.

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9. CONFLICT OF INTEREST

Conflict of interest declared none.

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