Evaluation of Potential Drug–Drug Interactions in the Prescriptions of Diabetic Inpatients, Seiyun City, Yemen

تقييم التداخلات الدوائية الدوائية المحتملة في وصفات مرضى السكري الرقود، مدينة سيئون، اليمن.

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Abstract

Background: Patients with diabetes often have coexisting chronic health conditions such as hypertension, dyslipidemia, coronary artery disease, depression, and chronic kidney disease. Drug interactions are a daily challenge for physicians and screening all drug interactions in the prescriptions has become very cumbersome and virtually impossible.

The aim and objective of our study is to estimate the prevalence of Drug–Drug Interactions (DDIs) in diabetic patients and raise awareness among physicians to prevent the occurrence of some clinical adverse events.

Method: This is a cross–sectional observational retrospective study design conducted on diabetic patients admitted to Seiyun Hospital over 2 months from December 2023 to Feburary 2024.

Results: This study found that approximately two–thirds of patients were prescribed more than six medications. Most prescriptions that were prescribed for diabetic patients have at least one or more Drug–Drug Interactions per prescription. We note that most of the antidiabetic agents that cause drug interactions with other medications were moderate and minor interactions; only six interactions of major type were observed with quinolone antibiotics.

Conclusions: This study found that the incidence of drug interactions in diabetic patients was very high. Therefore, the best way to avoid the occurrence of such drug interactions is to have a specialized pharmacist examine the total medication chart for each patient individually.

Keywords: Antidiabetic agents, Drug–Drug Interactions(DDI), Diabetic patients.

الملخص

الخلفية: يعاني غالبا مرضى السكري من أمراض مزمنة كارتفاع ضغط الدم، اضطراب شحوم الدم، مرض الشريان التاجي، الاكتئاب، ومرض الكلية المزمن. تمثل التداخلات الدوائية تحديا يوميا للأطباء؛ لأن فحص جميع التداخلات الدوائية في الوصفات الطبية أمرا مرهقا ومستحيلا للغاية. كان الهدف من دراستنا هو تقدير مدى انتشار التداخلات الدوائية عند مرضى السكري وأيضا لزيادة الوعي بين الأطباء لمنع حدوث بعض التأثيرات السريرية السلبية.

الطريقة: صممت دراسة رصدية استرجاعية مقطعية أجريت على مرضى السكري الرقود في مستشفى سيئون العام على مدى شهرين من ديسمبر ٢٠٢٣ إلى فبراير ٢٠٢٤.

النتائج: أظهرت هذه الدراسة أن ثلثي المرضى تقريبا وصفت لهم أكثر من ستة أدوية. تحتوي معظم كل وصفة من الوصفات الطبية الموصوفة لمرضى السكري على واحد أو أكثر من التداخلات الدوائية الدوائية. معظم التداخلات الدوائية عند مرضى الداء السكري كانت تداخلات دوائية من النوع الخفيف والمتوسط؛ بينما ستة تداخلات دوائية فقط كانت من النوع الخطير والتي كانت مع المضادات الحيوية من مجموعة الكينولون.

الاستنتاجات: إن معدل حدوث التداخلات الدوائية لدى مرضى السكري كانت مرتفعة جدا، لذلك فإن الطريقة المثلى لتجنب حدوث مثل هذه التداخلات الدوائية هو الاستعانة بصيدلاني متخصص لاستقصاء جميع وصفات الادوية لكل مريض داء سكري على حدة.

الكلمات المفتاحية: العوامل المضادة، التداخلات الدوائية الدوائية، مرضى السكري.

1. Introduction

Patients with diabetes often have to coexist with chronic health conditions such as hypertension, dyslipidemia, coronary artery disease, depression, and chronic kidney disease that may lead to macrovascular and microvascular complications, so the management of diabetes is considerably more complicated and the patients often use multiple medications. Further complications arise among patients when they fail to adhere to multiple medication prescriptions. Prevalence of 57%–84% of patients with diabetes using five or more medications (John *et al.*, 2018).

A drug interaction can be defined as a measurable modification of the action of one drug by prior or concomitant administration of another medication (Melmon; Morrelli, and Carruthe 2002). Drug interactions are a daily challenge for physicians and screening all interactions in the prescriptions has become very cumbersome and virtually impossible (Ament *et al.*, 2000).

These drug interactions become more common in diabetic patients who are administering many medications and have multiple comorbidities. (Tuladhar *et al.,*2021). Interactions between antidiabetic drugs show synergistic effects to each other and may increase the risk of hypoglycemia (Kumari, *et al.,*2023). Drug interactions are believed to occur in 3% to 7% of patients taking up to 10 medications and in as many as 20% of patients taking 10 to 20 medications. It is estimated that drug interactions cause up to 2.8% of all hospitalizations (Hogan *et al.*, 1999).

The significance of the research lies in the fact that diabetic patients have many comorbidity diseases in Yemen, and they get a large number of serious complications due to which they are admitted to hospital. So physicians describe several medications to treat and alleviate these complications, and thus these medications lead to a high incidence of drug interactions "One of the causes of adverse reactions in patients."

This study aims to estimate the prevalence of Drug–Drug Interactions

(DDIs) in diabetic patients and raise awareness among physicians to prevent the occurrence and recurrence of clinical adverse events.

2. Methodology

Study Area

The study was conducted at Seiyun General Hospital Authority of Hadramout state in Yemen.

Study Period

Data of this study were collected during the period of two months, from December 2023, up to March, February 2024.

Study Design

A hospital–based retrospective study has been designed by a descriptive cross–sectional manner.

Study Population

All diabetic patients attending and admitted to the internal department of medicine at the hospital during the settled period were included in this study as a study population.

Sample size

A total of 172 patients were admitted to the internal medicine department during the study period. There were 76 diabetic patients were included in this study.

Study Tools and Study Procedures

A standard data collection form was designed and used to collect the required data. The data were extracted from the patient's medical records and the collected data were divided into the following elements:

- **Demographic characteristics** such as age and gender; they were

recorded.

- **Clinical characteristics** included duration of hospital stay, presence of comorbidities, reason for admission, and past medical history.
- **Drugs prescribing**: name of drug, frequency, category of drugs.
- **Drug interactions**: presence of drug interaction, frequency, severity of drug interaction.
- We collected data about the patient by designing a questionnaire.
- Microsoft Office Excel database was created using these variables.
- Afterward, we classified and identified the patients, analyzed the types of drugs prescribed identified the drug class for each medication, and calculated the number of drugs for each patient as well as the type and number of drug–drug interactions.
- We classified the antidiabetic agents into four classes: insulin, sulfo-n=rmin, and Di peptidyl p$=384$ s.

Classification, Identification, and Analysis of Drug–drug Interactions

- Drug–Drug Interactions were checked and identified using a program (Drug Interactions Checker, available at https://www.drugs.com/drug_interactions.html)
- The Drug Interactions Checker requires the name of the drug and selects it from a list to confirm the choice.
- Multiple drugs can be searched for simultaneously and, when the list is complete, a drug interaction report is shown on the computer screen by pressing the check for interactions button.
- The drug interaction report classifies the results into major, moderate, and minor Drug–Drug Interactions.

Inclusion and Exclusion Criteria:

All diabetic patients, aged 18 years or above, who were admitted to the internal medicine department and received two or more drugs during their

hospitalization stay were analyzed for drug–drug interactions. Diabetic patients who were admitted to the internal medicine department and did not receive any drug were excluded from this study. All diabetic patients who received only one drug were also excluded from analyzing regard drug–drug interactions.

Ethical Consideration

Ethical approval and permission from the ethics committee of Seiyun General Hospital Authority were obtained before conducting the study.

Statistical Analysis

All data were analyzed by descriptive statistics as categorical variables (age group, gender, length of stay, comorbidity, polypharmacy, and drug interactions) which were presented as frequencies and percentages, and continuous variables (age, length of stay, polypharmacy, and drug interaction) which were presented as the mean with (SD).

The statistical software Statistical Package for Social Science (SPSS) version 26 (SPSS Inc., Chicago, IL, USA) was used to analyze all the data collected in this study.

3. Results

A total of 172 patients were admitted to the internal medicine department during the study period.

Over 2 months (December.2023 to Feburary.2024), **76** diabetic patients were included in this study. Out of them, **66** patients had at least one Drug–Drug Interaction.

3.1. **Characteristics of the Study Population**.

Table 1: Demographic and Clinical Characteristics (n=76)

Characteristic	NO	(%)
Gender		
Male	64	84
Female	12	16
(Age (year		
18–30	5	6.6
31–45	8	10.5
46–60	29	38.2
61 $\leq$	34	44.7
Mean ± S.D	15.9 59.4±	
(Length of stay (day		
3 >	50	65.8
3$\leq$	26	24.2
Mean ± S.D	3.59±3.8	
Total	**76**	**100**
Comorbidities		
Cardiovascular disease	66	87
Liver disease	8	11
Renal disease	8	11
Infection	5	7
GIT disease	5	7
Cancer	3	7
Others	4	5

3.2. **Drugs Prescribed vs. Drug Interactions**

During the study period, 76 prescriptions of diabetic inpatients were screened,
Out of them, 87% of prescriptions had at least one possible Drug–Drug inter-
action, Table 2

Table 2: **Prescriptions Screened**:

	NO	%
Prescription with drug interactions	66	87
Prescription without drug interactions	10	13

Table 3: **Number of drugs prescribed per prescription (n=76)**

Drugs Prescribed	NO	(%)
5–2	19	25
10–6	49	65
15–11	7	9
More than 15	1	1
(Mean(SD	7.33 ± 2.78	
Total	76	100

Table 4: **Number of Drug Interactions per Prescription (n=66)**

Number of Interaction	NO	(%)
1–2	8	12
3–5	14	21
6–10	27	41
15–11	9	14
More than 15	8	12
(Mean(SD	7.63±7.09	
Total	66	100

The mean number of Drug–Drug Interactions was 7.63±7.09 higher than the mean number of drugs prescribed which was 7.33±2.78. (Table 3&4)

It was found in this study that there were about **584** medications that were dispensed and caused about **557** Drug–Drug Interactions for diabetic patients, regardless of the frequency of some classes of drug and DDI in most prescriptions, see Table 5.

Table 5: **Main classes of drugs prescribed**

Class of drug	NO	%
Antibiotics	107	18
Antiplatelet	74	13
Antidiabetic agents	67	11
Proton pump inhibitor	57	10
Anticoagulants	43	7
Antihyperlipidemic	40	7

Analgesic	36	6
Diuretics	34	6
Beta–adrenergic blocker	23	4
ACEI\ARBs	23	4
Adrenergic agnoist	9	2
other	71	12
Total	**584**	**100**

Drug–Drug Interactions were classified based on their pharmacological effects and severity into **major**, **moderate**, and **minor** drug interactions. Of the **577** Possible Drug–Drug Interactions in our study, moderate drug interactions were most common in diabetic patients at 412 times (71%) of the total pDDIs, inter–actions with major severity accounted for approximately 58 (10%) and minor severity interactions accounted for approximately 107 (18%). (Fig.1)
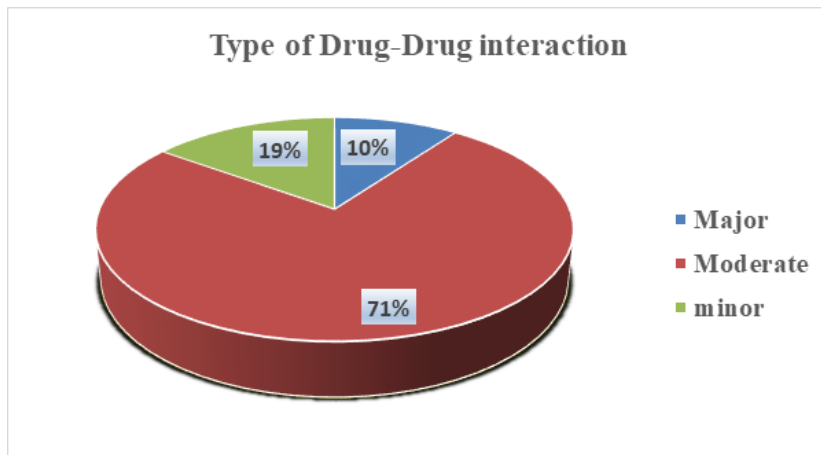

Figure 1: **Classification of Drug Interaction**

3.3. Antidiabetic Agents in Diabetic Patients

Antidiabetic agents were prescribed 67 times, with insulin as the most frequent agent employed alone or in combination with other drugs.43% of the prescriptions received oral Antidiabetic agents, Table 6.

Table 6: Antidiabetic agents prescribed cause interactions

Antidiabetic agents	Drug Prescribed		Drug interaction	
	NO	%	NO	%
insulin	38	57	59	46
Sulfonyleurea(glimepiride, (glibenclemide, gliclazide	14	21	34	27
metformin	11	16	28	22
Di peptidyl peptidase–4 inhib–(itors (sitagliptin	4	6	7	5
Total	**67**	**100**	**128**	**100**

There were Drug–Drug Interactions between antidiabetic themselves or with other non– antidiabetic agents. Table 7

Table 7: Drug interaction of antidiabetic agents(n=128)

Antidiabetic agents	NO	%
Drug interactions between antidiabetic agents themselves	35	27
Drug interactions with non–antidiabetic agents	93	73

Regarding the antidiabetic agents prescribed specifically for DM, We note that most of the antidiabetic agents that cause drug interactions were moderate types, while others were minor types; there were only six major drug interactions that were observed with quinolone antibiotics. (Insulin with ciprofloxa-

cin, levofloxacin, moxifloxacin and glyclizide with levofloxacin), See Table 8.

Table 8: **Classes of Drugs that Cause Interaction with Antidiabetic Agents**:

Non–antidiabetic drug	Antidi–abetic drug	NO	Potential inter–action(s)	Severity of DDI
(**Salicylate**(aspirin	Insulin	22	↑ risk of hypogly–cemia	Moderate
	glimepiride	4	↑ effect of antidia–betic agents	Moderate
Diuretics(furosemide, toresamide, hydro–(chilorothiazide	All	14	↓ effects of antidi–abetic agents	Moderate
BB (carvedilol, bisop–(rolol, metoprolol	Insulin	10	↑ risk, severity, and duration of hypoglycemia	Moderate
	Sulfony–lurea	3	↑ risk of hypogly–cemia	Moderate
ACEI\ ARBs captopril, lisinopril,) (losartan	All	10	↑ risk of hypogly–cemia	Moderate
Adrenergic agonists (dopamine, salbu–(tamol	All	6	Reduced effects of antidiabetic agents	Moderate
Corticosteroids dexamethasone,) prednisolone, hydro–(cortisone	All	5	Reduced effects of antidiabetic .agents	Moderate

Fluoroquinolone (ciprofloxacin, levo–floxacin, moxifloxacin)	Insulin	4	Disturbs blood glucose hemosta–sis.	Major
	Sulfony–lurea	2		Major
	Metformin	3		Moderate
	Di pepti–dyl pep–tidase–4 inhibitors	2	Disturbs blood glucose hemosta–sis.	Moderate
sucralfate	All	3	Affect the absorp–tion of antidiabetic agents	Moderate
Linezolid	Insulin	1	↑ risk of hypogly–cemia	Moderate
	Sulfony–lurea	1		Moderate
Warfarin	metformin	1	Disturbs blood glucose and re–duces the effect of warfarin	Moderate
PPI(esomeprazole only)	Sulfony–lurea	1		Minor
clopidogrel	Sulfony–lurea	1		Minor
Total		**93**		

3.4. **Major Drug–Drug Interactions in Diabetic Patients**:

In this study, it was noted that there are 58 major drug interactions, see Figure 1. Most of the serious or major interactions observed between drug interactions were antiplatelet agents (aspirin and clopidogrel) and anti–coagulant agents (clexan), See Table 9.

Table 9: **The most major Drug–Drug Interactions encountered by diabetic patients**

Drug name		NO	(Potential interaction (s	Severity of drug in–teraction
Drug 1	Drug 2			
Aspirin	Clexan	17	risk of bleeding ↑	Major
Clexan	Clopidogrel	16	risk of bleeding ↑	
Ceftriaxone	Ca– gluconate	7	Can form crystals when mixed in solution or bloodstream	
Salbutamol	Carvedilol	2	Oppositive effect on the body	
Insulin	Ciprofloxacin	2	Disturbs blood glucose hemostasis	
Insulin	Levofloxacin	2	Disturbs blood glucose hemostasis	
Warfarin	Moxifloxacin	2	risk of bleeding ↑	
Warfarin	Clexan	2	risk of bleeding ↑	
Warfarin	Metronidazole	1	risk of bleeding ↑	
Insulin	Moxifloxacin	1	Disturbs blood glucose hemostasis	
Gliclazide	Levofloxacin	1	Disturbs blood glucose hemostasis	
Levoflox–acin	Prednisolone	1	risk of Tendinitis and tendon ↑ rupture	
Levoflox–acin	Tramadol	1	risk seizures ↑	
Plasil	Tramadol	1	risk seizures ↑	
Lisinopril	Losartan	1	Side effects (BP, hyperkalemia, ↑ (kidney function impairment	
Spironolac–tone	Losartan	1	hyperkalemia ↑	
Total		**58**		

4. Discussion

In this study, over two consecutive months, we took patient records from the Department of Internal Medicine at Seiyun Teaching Hospital (men and women) and recorded the diseases diagnosed by the physician. Then we wrote down all the prescribed medications for each patient, whether they were anti-diabetes agents or others, knowing that there were patients with diabetes, but who were not prescribed antidiabetic drugs, given that they were continuing the same previous treatment and the physician did not want to record the medications in the file again.

In this study, we found that the proportion of men is greater than that of women; unlike other studies that prove the opposite or that the proportion is equal (Dobrica *et al.*, 2019), but this is not accurate for other reasons (as outlined in Table 1).

As for age, all patients included in the study were over 18 years old; after that, we divided them into many age groups and found that most diabetic patients fall under the age group over 61 years, where the average age was 59 years, as the age group over 61 years is the most dispensing of medications (more than ten medication) (as shown in Table 1).

As for drug interactions, it was noted that the age group 61 ≤(y) is the most frequent with 10 drug interactions, as it is the most prescribed drug, followed by the age group (40-60y) with five drug interactions. We compared these results with a study conducted by Kohler in which the average age of patients who experienced drug reactions was 64.8 ± 9.7 years (Kohler *et al.,*2000). In general, the literature reveals that as age increases, the probability of drug interactions also increases (Kohler *et al.*,2000; Juurlink *et al.*,2003).

As for the relationship between the patient's stay in the hospital with the occurrence of drug interactions, we found that there is not a relationship. This

study differs from previous studies that said that there was a positive relationship between the length of stay in the hospital and the occurrence of drug interactions (Riechelmann *et al.,* 2008).

In addition to diabetes which may be the cause of the patient's admission to the hospital, the diseases of the circulatory system come in the foreground first, such as hypertension, arteries, and strokes (Table 1). In previous studies, the most common co-morbidity was hypertension, followed by dyslipidemia and diabetic complications (Kohler *et al.,* 2000; Egger, Drewe, Schlienger, 2003).

Through the study, it was found that most prescriptions contain at least one drug interaction, as outlined in Table 2, and this explains to us that drug interventions inevitably occur in patients with diabetes; this completely coincides with a study done by Doubova, which said that more than 80% of prescriptions contain more than one drug interaction. (Doubova *et al.*, 2007).

In this study, as outlined in Table 3, it was found that nearly two-thirds of the patients were prescribed 6–10 medications, and some patients were given more than 10 medications, where the average number of medications prescribed to each patient was six medications.

As shown in Table 5, the most classes prescribed were antibiotics, especially ceftriaxone, then Antiplatelet (aspirin), and then antidiabetic agents (insulin and oral). This study was consistent with a study conducted by Sanker that more than half of prescriptions contain antibiotics. (Sankar *et al.*,2015). On the other hand, there is a study in 2019 by Dobrica; it showed that the most common medication classes prescribed to diabetic patients were statins, diuretics, beta–blockers, and angiotensin–converting enzyme (ACE) inhibitors(Dobrica *et al.,* 2019).

It was found that the average number of Drug–Drug Interactions for a patient is slightly more than the average number of drugs prescribed to the same

patient, and this explains that some drugs may interact with all drugs of one prescription, as the study showed that nearly half of patients have (6–10) drug interactions(Table 4).

As shown in Figure 1, and according to (www. drug.com) program, the interactions were divided into three types, according to their dangers to the patient, as it was found that approximately three-quarters of Drug–Drug Interactions had moderate interactions, while 10% of patients have major drug interaction. These results are similar to other results reported in previous studies, although different methods of classifying drug interactions were used, which make comparison difficult (Cruciol–Souza, Thomson, 2006; Vonbach,2008; Kumari, *et al*.,2023). Antiplatelet drug interactions come first among them to cause severe drug interactions such as bleeding and others. As for anti–diabetes agents, their interaction with quinolone antibiotics may constitute a severe interaction.

Anti–diabetes agents interact with a large number of drugs (as outlined in Table 8), so the physician must know this drug interaction to avoid it or choose the best alternative to this medication. This reinforces the importance of having a clinical pharmacist in our hospitals to improve health care for patients. Anti–diabetes drugs, especially insulin, come first to cause drug interactions regardless of their severity with aspirin followed by diuretics and anti–hypertensive drugs of all types, then antibiotics(quinolone).

5. Conclusions

This study showed that the incidence of pDDIs is high. We found that most prescriptions contain five or more drug interactions, and this explains to us that drug interventions inevitably occur in patients with diabetes. It was observed that the prevalence of DDIs increased linearly with the number of drugs and age. The majority of interactions were pharmacodynamics in nature, having moderate severity, and there were major drug interactions. Therefore, it requires intensive monitoring during therapy in diabetic patients. The physician must know the interactions between medications, especially the major ones, to avoid dispensing them or know their side effects to treat them. The most appropriate approach to avoiding drug interactions is for a hospital pharmacist to screen the total medication chart of every individual patient.

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