RESEARCH ARTICLE

Evaluation of Drug Interactions with Medications Prescribed to Ambulatory Patients with Metabolic Syndrome in Urban Area

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This study is planned to assess the profile of drug-drug interactions in the medications prescribed to metabolic syndrome patients and also to identify the possible predictors for potential drug-drug interactions.
Materials and Methods: A cross-sectional study was conducted from 25th Jan to 1st April 2019 to check the drug interactions in ambulatory metabolic syndrome patients in Jeddah, Saudi Arabia. A sample size of 142 patients was included in the study. The prescriptions were analyzed for potential drug interactions using Lexi-Interact Online and Medscape online software to check drug-drug interactions.
Results: It is observed that as an average 3.85 drug per prescription was prescribed. We observed 55 prescriptions are containing incomplete patient information that is 48.6% of prescriptions. The 62% of patients of this study were more than 60 years. We found a maximum number of prescriptions were found 4-6 drugs per prescription 60.56 % and 78.12 % interactions were moderate interaction and 3.9 % interaction found were major interactions.
Conclusion: It was observed that the number of DDIs increased linearly with the number of drugs and age. The majority of interactions was pharmacodynamic in mechanism and showed moderate severity.

Introduction

Metabolic syndrome was first recognized by the medical community and was characterized by the clustering of abdominal obesity, elevated blood pressure, hyperglycemia, and dyslipidemia [**1**]. Gulf countries have shown a prevalence of metabolic syndrome that ranges from 17% in Oman [**2**] to 40.5% in the United Arab Emirates (UAE) [**3**], in Saudi Arabia reported it to be 39.3% [**4**].

Metabolic syndrome is a serious condition, it can reduce the risks by non-pharmacological management like reducing the weight; increasing the physical activity; eating a heart-healthy diet that's rich in whole grains, fruits, vegetables and fish along with pharmacological treatment with multiple drugs (polypharmacy) for associated co-morbidities like blood glucose, blood cholesterol, and blood pressure.

Diabetes is metabolic disorder associated with hyperglycemia, about 95% of the diabetic patients are type-2 diabetes. The excessive prevalence of diabetes notice in Saudis could be on the basis of ethnicity, obesity, life style and positive family history [**5,6**].

International Diabetes Federation Atlas in its sixth edition in the year 2013 grade Saudi Arabia the 7th in the top ten countries known for their high diabetes prevalence, and this place is presume to be the sixth by 2035 [**7**].

Alteration in the efficacy of one drug due to the presence of another simultaneously administered drug is termed as drug-drug interactions (DDIs). This alteration is mostly quantitative, i.e., the response to a drug is either increased or decreased in intensity. Drug therapy is an integral part of patient management. Though the use of multiple drugs may be required either to manage a metabolic syndrome or comorbidities, harmful interactions may occur between these drugs.

The drugs most commonly implicated in major potential interactions are those used in the day-to-day clinical management of metabolic syndrome patients [**8**]. Hence, this study is planned to assess the profile of drug-drug interactions in the medications prescribed to metabolic syndrome patients and also to identify the possible predictors for potential drug-drug interactions in the metabolic syndrome patients.

Materials and methods

A cross-sectional study was conducted from January to April 2019 to check the drug interactions in ambulatory metabolic syndrome patients in Jeddah, Saudi Arabia. The

study includes patients of either sex from outpatient clinics. The patients admitted to the hospital are excluded from the study. The patients were also asked for their medication adherence and data was collected from medical prescriptions and patients' medical records of different out-patient clinics.

A sample size of 142 patients was included in the study. The data collected included demographic characteristics such as age, gender, height, weight, medical history, and medications prescribed. The prescriptions were analyzed for potential drug interactions using Lexi-Interact Online and Medscape online software.This software provides the severity rating and the summary of drug-drug interactions. The severity rating is categorized as a major, moderate and minor drug interaction. Monitoring of therapy is recommended for the category of major where there is evidence of potential interaction which is clinically significant.

In this study were carried out to evaluate the drug interactions by using various drug interaction checkers like Lexicomp and Medscape databases.

All statistical analyses were performed using Graphpad Prism software, version 8. Both descriptive and analytic statistics were applied, descriptive statistics were used to describe continuous (Mean ± SD) and categorical variables (frequency and percent). The study was approved by the IEC of the College of Ibnsina national college for Medical studies, Jeddah.

Results

Total numbers of prescriptions were one hundred and forty-two included in this study. Itwas found that an average number of 3.85 drugs were prescribed per prescription as shown in **Table 1.** The total number of interaction was found to be five hundred twelve.

Table 1. General characteristics of study subjects.

Characteristics	Number of prescriptions	Per-centage	Mean ± SD	P value
Gender				
Male	98	69.02		
Female	44	30.98		
Age in years				
0 – 30 years	2	1.4	25 ± 4.3	---
31 – 60 years	52	36.6	57.6± 2.84	0.002*
>60	88	61.9	71.3± 5.98	0.003*
Prescribed medications per prescription				
≤ 3	48	33.8	2.1 ± 0.87	0.20
4 – 6	86	60.56	4.6 ± 0.7	0.51
>6	8	5.63	6.25± 0.46	0.16
Total Number of drugs prescribed	546 --------			
Average drugs prescribed per prescription	3.85 -------			

*Significant difference (P < 0.05).

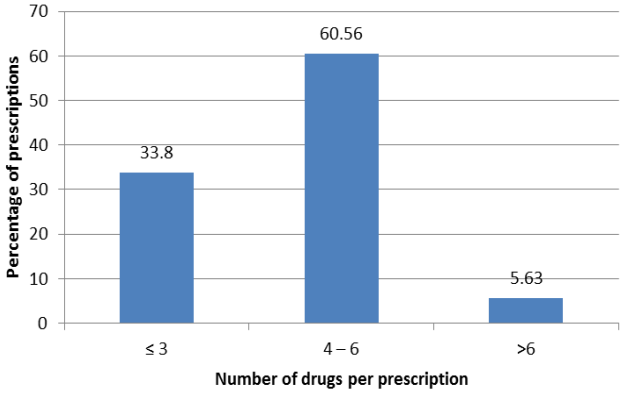

Fig. 1. Prescribed medications per prescriptionshow maximum number of prescriptions were found 4-6 drugs per prescription 60.56 %.

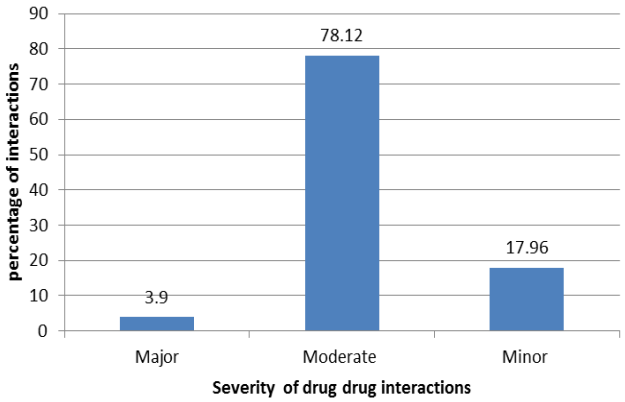

Fig. 2. Illustrate percentage severity of drug-drug interactions 78.12 % interactions were moderate interaction and 3.9 % interaction found were major interactions.

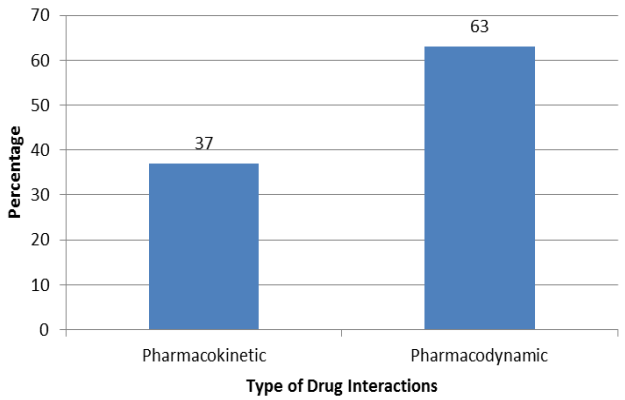

Fig. 3. Shows distribution of drug interactions based on the mechanism (pharmacokinetic and pharmacodynamic interactions).

The maximum number of drug interactions based on mechanism was found as pharmacodynamics interaction 63% as shown in **Fig. 3**.

One hundred forty-two patients were included in this study over three months out of which 69% were males and 31% were females the data was collected from the different outpatient clinics of tertiary care hospitals in Jeddah city. An average of 3.85 drugs per prescription was prescribed and fifty-five prescriptions were with incomplete patient information that was 48.6% of

prescriptions. Sixty-two percent of patients of this study were more than 60 years.

Table 6 describes about the clinical characteristics of the study population, like mean BMI, number of patients with diabetic, patients with hypertension and hyperlipidemic and number of patients with diabetic and hypertension. The maximum BMI was found in age group of patients 41 to 60 years. The maximum number of diabetic patient (28.2%) were found in age group 61 to 80 years. 29.6% patients were found with hypertension and hyperlipidemic comorbidities. 27.5% study population had diabetic with hypertension.

Discussion

Saudi Arabia is known to be one of the top countries worldwide with a high prevalence of diabetes, and a similarly high rate of obesity that has a direct effect on more than one-third of its adult population [**9**]. Also, the prevalence of other components of metabolic syndrome is reaching soaring heights in the Kingdom [**4**]. Therefore, with such a high prevalence of the assorted elements of metabolic syndrome, the prevalence of metabolic syndrome in Saudi Arabia would be expected to exceed that is reported in other countries. DDIs are becoming a serious issue with complex drug therapies. This can result in anything from minor morbidities up to fatal consequences. They are attributed to polypharmacy and noncompliance of the patients [**10-12**]. In the present study, we found that the frequency of major drug-drug interactions was 3.9% in patients receiving drugs at outpatient clinics.

These potential DDIs suggest that there is a need for modification or alteration of therapy such as dosage adjustment. To prevent these DDIs, health care providers should have adequate information about DDIs not only via drug information center which can provide evidence-based information to health care professionals but also through encouraging the empowerment of clinical pharmacists that can provide an evidence-based approach to drugs and thereby prevent drug therapy problems of which DDIs is one. This study also found that 63% of the DDIs were of pharmacodynamic type. For example, the DDI between aspirin and captopril is known to have decreased renal effect. This suggests the need for counseling the patients who are at risk for experiencing these DDIs, such as elderly and patients with renal insufficiency.

We observed the majority of prescriptions were containing four to five drugs that are found in eighty-six prescriptions (**Table 1**) around eight prescriptions are having more than six drugs. A total number of drugs prescribed in one hundred forty-two prescriptions contain five hundred forty-six drugs out of which 34.8% drugs were cardiac drugs, 14.7 % endocrine drugs, 13.2% anti-platelets as the highest drugs prescribed and other categories of drugs prescribed were shown in **Table 2**. Moderate type of drug-drug interactions observed in maximum number as seventy-eight percentage, major interaction was found 3.9 % and minor interactions were around 18% presents in **Table 3**. Distribution of potentially interacting drug pairs with their clinical significance and possible adverse outcomes were shown in **Table 4**.

Table 2. Category of drugs prescribed.

Category	Number of drugs	Percentage of drugs
Cardiac drugs	190	34.8
Antihyperlipidemic	52	9.5
Endocrine drugs	80	14.7
Proton pump inhibitor	50	9.2
Anti-cholinergic	8	1.5
Anti-platelets	72	13.2
Vitamins	44	8.1
NSAIDs	20	3.7
Antibiotics	6	1.1
Antivirals	2	0.4
Antiemetic	8	1.5
H1 antagonists	10	1.8
Antiepileptic	4	0.7

Table 3. Patterns of Drug-Drug interactions by clinical significance.

Pattern	Frequency	Frequency in Males	Frequency in Females	Sum of Percentage
Severity				
Major	20	18	2	3.9
Moderate	400	350	50	78.12
Minor	92	90	2	17.96

Table 4. Distribution of potentially interacting drug pairs with their clinical significance and possible adverse outcomes.

Drug Pairs	Frequency	Clinical significance	Possible adverse outcomes
Aspirin-Ramipril	4	Major	Significant Decrease in renal functions
Ceftriaxone - Enoxaparin	2	Major	Significant Increase anticoagulation
Omeprazole - Digoxin	2	Major	Digoxin toxicity
Omeprazole-Clopidogrel	2	Major	Significant decrease anticoagulation
Fenofibrate - Rosuvastatin	4	Major	Increase the risk for rhabdomyolysis
Perindopril-Aspirin	4	Major	Significant Decrease in renal functions
Clopidogrel - Esmoprazole	2	Major	Significant decrease anticoagulation

Drugs with the probability of causing drug-drug Interactions shown in **Table 5** the maximum number of drug interactions were found with aspirin as twenty-two percent and the second-highest was with bisoprolol that is around ten percent and with other drugs show in **Table 5**.

Table 5. Drugs with probability of causing drug interactions.

Drug	Frequency	Percent (%)
NSAIDs	36	7.03
Captopril	26	5.08
Aspirin	114	22.27
Telmesartan	20	3.91
Olmesartan	12	2.34
Omeprazole	6	1.17
Clopidopril	8	1.56
Valsartan	38	7.42
Bisoprolol	52	10.16
Amlodipine	6	1.17
Glimpride	6	1.17
Pantoprazole	2	0.39
Irbesartan	18	3.52
Metformin	2	0.391
Hydrochlorothiazide	22	4.3
Ceftriaxone	10	1.95
Enoxaparin	20	3.9
Digoxin	24	4.7
Esmoprazole	20	3.9
Perindopril	12	2.34
Fenofibrate	10	1.95
Statins (HMG CoA inhibitors)	34	6.64
Insulin	14	2.73

Table 6. Clinical characteristics of the study population.

Age group in years	Number of Patients	Mean BMI (Body Mass Index) ± S.D.	Number of Patient with diabetes (Percentage)	Number of Patient with hypertension and hyper-lipidemic (Percentage)	Number of Patient with diabetes and hypertension (Percentage)
0-20	2	30 ± 4.3	--	2 (1.4%)	0
21- 40	13	29 ± 4.5	9 (6.3%)	4 (2.8%)	7(4.9%)
41-60	39	34 ± 5.1	27 (19 %)	12 (8.5%)	11(7.7%)
61-80	82	32 ± 3.9	40 (28.2%)	42 (29.6%)	39(27.5%)
81-100	6	31 ± 5.4	4 (2.8%)	2 (1.4%)	2(1.4%)

The drug interactions based on the mechanism in the highest percentage were pharmacodynamic interactions in sixty-three percent and pharmacokinetic interactions were in thirty-seven percent were shown in **Fig. 3**. The risk of DDI was significant due to multiple drug therapy along with co-morbidities in patients more than forty years of age. Similar observations have been reported **[13-16]**. However, their potential to cause serious DDI has been neglected by prescribers. This calls for educating prescribers regarding DDI and undertaking a prescription audit regularly. Our study had few limitations such as we could not assess the actual impact of DDIs and while assessing the rationality and DDIs, the clinicians' viewpoint was not taken into account, which could have been different than ours.The study has a few limitations like the study was conducted only in a few OPD clinics with limited sample size and time limitation. All the study patients were observed obese with Body Mass Index (BMI) an average of 31.2.

Descriptive statistics were performed to describe continuous (Mean ± SD) and categorical variables (frequency and percent) P-value was found significant.

Conclusion

It was observed that the number of DDIs increased linearly with the number of drugs and age. The majority of interactions was pharmacodynamic in mechanism and showed moderate severity. This study providedreference data for the surveillance of DDIs in ambulatory metabolic syndrome patients from different OPD clinics of Jeddah. Finally, correct stress ought to tend to drug information center and clinical pharmacy services at primary centers and OPD clinics, which might play a vital role inminimizing DDIs in metabolic syndrome patients by providing DDI-related information to prescribers. Wealso recommend developinga collaborative, patient-centered approach in the education of pharmacy professionals to deliver effective drug therapy so the incidence of drug therapy problems will be minimized.

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Keywords

Drug interactions, ambulatory patients, metabolic syndrome.

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References

1. Reaven, G.M. *Diabetes*, **1988**, *37*, 1595.
2. Al-Lawati, J.A.; Mohammed, A.J.; Al-Hinai, H.Q.; Jousilahti, P.; *Diabetes Care*, **2003**, *26*, 1781.
3. Malik, M.; Razig, S.A.; Metab. Syndr. Relat. Disord., **2008**, *6*, 177.
4. Al-Nozha, M.; Al-Khadra, A.; Arafah, M.R.; Al-Maatouq, M.A.; Khalil, M.Z.; Khan, N.B.; et al. *Saudi. Med. J.*, **2005**, *26*, 1918.
5. Bener, A.; Hussain, R.; Teebi, A.S. Consanguineous marriages and their effects on common adult diseases: studies from an endogamous population. *Med. Princ. Pract.*, **2007**, 16, 262.
6. Al-Gazali, L.; Hamamy, H.; Al-Arrayad, S.; *B.M.J.*, **2006**, *21*, 831.
7. International Diabetes Federation. IDF Diabetes Atlas [Internet]. 6th ed. Brussels, Belgium: International Diabetes Federation; **2013**. Available from: http://www.idf.org/diabetesatlas
8. Teixeira, J.J.V.; Crozatti, M.T.L.; dos Santos, C.A.; Romano-Lieber, N.S.; Potential drug-drug interactions in prescriptions to patients over 45 years of age in primarycare, Southern Brazil, **2012**, 7(10).
9. Al-Nozha, M.M.; Al-Mazrou, Y.Y.; Al-Maatouq, M.A.; Arafah, M.R.; Khalil, M.Z.; Khan, N.B.; *Saudi. Med. J.*, **2005**, *26*, 824.
10. Pouleur, H.; Etienne, J.; Van Mechelen, H.; Van Eyll, C.; Charlier, A.A.; Brasseur, L.A.; *Postgrad. Med. J.*, **1984**, *60*, 23.
11. Obreli-Neto, P.R.: Nobili, A.; de Lyra Júnior, D.P.; Pilger, D.; Guidoni, C.M.; de Oliveira Baldoni, A, et al. *J. Pharm. Pharm. Sci.*, **2012**, *15*, 332.
12. Banerjee, A.; Mbamalu, D.; Ebrahimi, S.; Khan, A.A.; Chan, T.F.; *Int. J. Emerg. Med*. **2011**, *4*, 22.
13. Janchawee, B.; Wongpoowarak, W.; Owatranporn, T.; Chongsuvivatwong, V.; *J. Clin. Pharm. Ther.*, **2005**, *30*, 13.
14. Patel, P.S.; Rana, D.A.; Suthar, J.V.; Malhotra, S.D.; Patel, V.J.; *J. Basic Clin. Pharm.*, **2014**, *5*, 44.
15. Lin, C.F.; Wang, C.Y.; Bai, C.H.; *Drugs and Aging*, **2011**, *28*, 219.
16. Maher, R.L.; Hanlon, J.T.; Hajjar, E.R.; *Expert Opinion on Drug Safety*, **2014**, *13*, 57.