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A PROSPECTIVE STUDY ON DRUG-DRUG INTERACTIONS IN DIABETIC PATIENTS AT TERTIARY CARE TEACHING HOSPITAL

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ABSTRACT

Diabetes is the most common disease. It is considered as one of the great global health challenges of the twenty-first century. The countries with the highest number of adults with diabetes include China, India, and the USA. Drug interaction is described as the change of the impact of the drug prior or concomitant administration of some other drug. Diabetic patients frequently have a number of other coexisting health problems. Therefore, in addition to anti-diabetic drugs, other medications are often needed to control these problems. The chance of drug interaction increases exponentially polypharmacy given to a patient. Main aim and objective of our study was to estimate the influence of probable drug-drug interactions, to identify the therapeutic class of the drug carrying a higher threat for drug-drug interactions and high-risk drugs accountable for drug-drug interactions and to find the common interactions between two anti-diabetic agents. The data collected included in-patient number, gender, age and drug prescribed. Interactions between other therapeutic class of drugs and insulin was found in 8 prescriptions. 17 Prescriptions had 23 major interactions between the drugs (5.51%). Aspirin was seen to be interacting with Glimepiride and Telmisartan in each 14 prescriptions. Poly-

pharmacy is a region of serious problem in diabetes mellitus, specially in the elderly patients. The best way to reduce the frequency of drug-drug interactions is to minimize the various other unnecessary drugs prescribed. To decrease the frequency of possible interactions it ought to be necessary to make a careful resolution of therapeutic alternatives.

KEYWORDS: Diabetes Mellitus, Insulin, Metformin, Drug-Drug interaction.

INTRODUCTION

Diabetes is the most common disease. Firstly the presence of sugar in the urine of Diabetics was indicated by Dobson in 1755. In 1989 von Mering and Minkowski that pancreatectomised dose become diabetic in addition to evolving digestive disturbances.[1]

It is a group of metabolic disorder characterized by high blood sugar level. It is classified into two types:

a) Diabetes mellitus: It is a group of metabolic disease in which an individual suffered from blood sugar level. Blood glucose is the main source of energy and comes from the food you eat. Insulin hormone made by the pancreas helps glucose from food get into your cell to be used for energy. The normal blood glucose level in human ranges between 70 to 90 mg per 100 ml. Hyperglycaemia is characterized by more than normal concentration of sugar level. Hypoglycaemia develops when sugar level falls below the normal range.
b) Diabetes insipidus: Diabetes insipidus is relatively rare disorder that does not affect blood glucose level but, just like diabetes mellitus, also causes increased urination. It obtained polyuria and polydipsia disease.

The American Diabetes Association has classified diabetes into the following categories:

a. Type 1 diabetes (T1D) “due to autoimmune beta cell destruction leading to absolute insulin deficiency”
b. Type 2 diabetes (T2D) “due to progressive loss of beta-cell insulin secretion frequently on the background of insulin resistance”
c. Gestational diabetes mellitus (GDM) as “diabetes diagnosed in the second or third trimester of pregnancy that was not clearly overt diabetes prior to gestation” and
d. Specific types of diabetes due to other causes (example- monogenic diabetes syndromes. It is important to understand the impact of each of these types of diabetes on QoL in order to attain the best outcomes for all patients.

Drug interaction is described as the change of the impact of the drug prior or concomitant administration of some other drug. Perhaps drug interaction either amplify or decrease the meant effect of one or each drug.[3]

High frequency of prescription of tablets with plausible drug interactions is common in primary care level; the best way to reduce the frequency of them is to minimize the variety of drugs prescribed.

The chance of drug interaction increases exponentially with the number of drugs given to a patient. Without a well-designed, computerized drug interplay monitoring system or a suited database, the investigation of incidences of drug interactions in prescription in medical institution is limited and the consequential development of a complete surveillance software for drug interactions in hospitals is no longer feasible.[5]

Nevertheless, now and again it is challenging to decrease the number of tablets prescribed for patients with more than one continual condition; therefore, to decrease the frequency of possible interactions it ought to be necessary to make a careful resolution of therapeutic alternatives, and in cases besides different options, patients must be trying to determine the frequency of potential drug-drug and drug-disease interaction in prescriptions of ambulatory and inpatients over 18 years of age, who will be visiting Srinivas hospital Mukka.

MATERIALS AND METHODS

Inclusion criteria

- Patients of age above 18 years.
- Diabetic Patients with multiple and chronic disease.
- Polypharmacy.

Exclusion criteria

- Patients of age below 18 years.
- Critically ill and ICU patients.
- Gestational diabetic patients.

Study methods

The study was based on random sample of 100 patients at Srinivas Institute of Medical Science and Research Centre Mukka.

The data of Drug – Drug interactions was collected from the patients via medical records of in-patients in a tertiary care hospital through data collection form, Interactions reporting form and drug treatment chart.

Data collected include in-patient no, gender, age and drug prescribed.

The questionnaires of data on drug intake contained data on the type of drugs taken, their dose, intake frequency, of the patient will be included.

In case of DDI the prescription of the subjects was reviewed and the interactions between the drugs was be found through interactions checker software.

The frequency of the drug taken was be considered.

Drug- Drug interaction severity was classified as major, moderate & minor.

Major DDI may be life-threatening and medical intervention may be necessary to minimize or prevent serious adverse effect.

Moderate DDI may result in an exacerbation of the patient's condition and may require an alternation in therapy.

Minor DDI have limited clinical effects.

Drug Interaction Assessment was categorized into Definite/certain, Probable, Suspected, Possible, Unlikely, according to WHO causality assessment scale.

RESULTS

Number of interaction found in age groups

Age group between 18-38 had 34 interactions(12.94%), 168 interactions were observed between the age group 39-58 (40.28%), between the age group 59-78 158 interaction were seen (37.88%) above the age 79 7 interactions were observed (1.67%).

Table 1: Number Interactoon found in age group.

Age Group	Number of interactions	%
18-38	54	12.94%
39-58	168	40.28%
59-78	158	37.88%
Above 78	7	1.67%

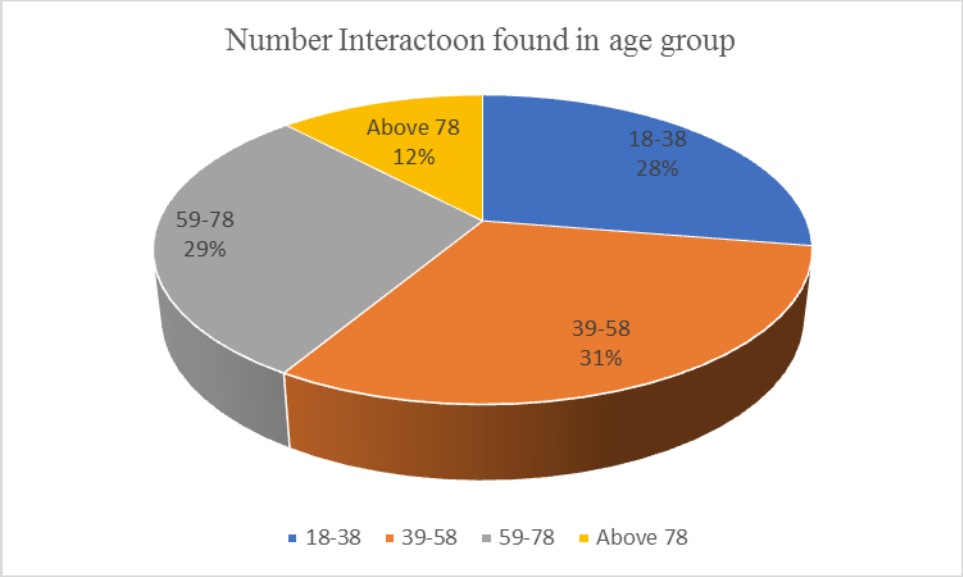

Fig. 1: Number Interactoon found in age group.

Interaction Severity

The severity of the Drug-Drug interactions was grouped in to 3 categories, they are Major, Moderate and Minor.

Out of the 100 prescriptions, it was noticed that 23 major interactions occurred in 17 prescription (5.51%).

96 Prescriptions had moderate interactions between drugs, the total number of moderate interactions between the drugs were 317 (76.01%).

41 prescriptions had 77 minor drug-drug interactions (18.48%).

Examples: Major Interactions between Glimepiride and Levofloxacin.

Moderate interactions between Insulin and Levofloxacin.

Minor interaction between Glimepiride and Clopidogrel.

Table 2: Interaction severity.

Interaction Severity	Total number of interactions	Percentage (%)
Major	23	5.51%
Moderate	317	76.01%
Minor	77	18.46%

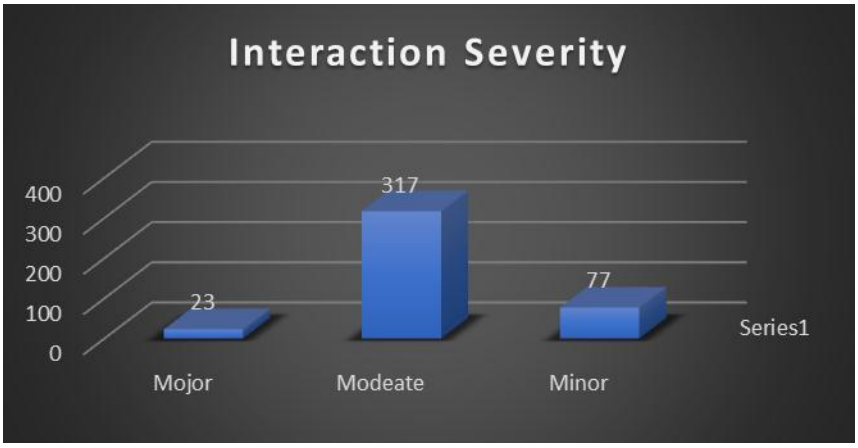

Fig. 2: Interaction Severity.

Common Interacting Pairs of Drugs

Aspirin was seen to be interacting with clopidogrel, insulin, glimepiride, telmisartan 9, 10,14 & 14 prescriptions respectively. Other drugs interacting were metformin & glimepiride in 11 prescriptions, insulin and metformin in 6 prescriptions.

Table 3: Common Interacting Pairs of Drugs.

	Drugs	Number of times seen interacted
Aspirin	Clopidogrel	9
Metformin	Glimepiride	11
Aspirin	Insulin	10
Insulin	Metformin	6
Aspirin	Glimepiride	14
Telmisartan	Aspirin	14

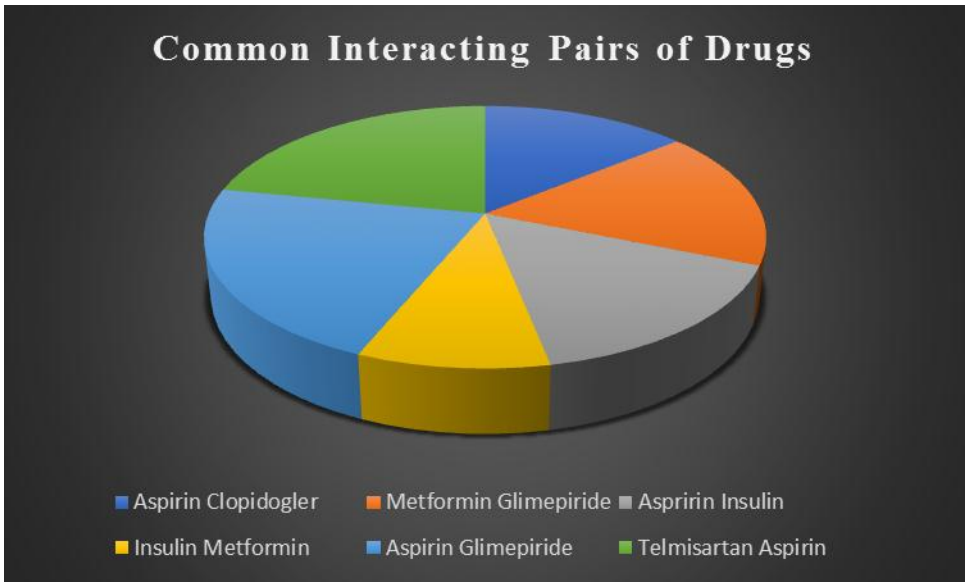

Fig. 3: Common Interacting Pairs of Drugs.

Top 5 drugs with high possibility of causing DDI's

Aspirin was seen having interactions 71 times (21.38%). Glimepiride had interactions 59 times (17.77%). Insulin had interactions 57 times (17.16%). Metformin and Budesonide were seen having interactions 49 times (14.75%) & 29 (8.73%) respectively.

Table 4: Top 5 drugs with high possibility of causing DDI's.

Ranking	Drugs	Number of times interacted	Percentage
1	Aspirin	71	21.38%
2	Glimepiride	59	17.77%
3	Insulin	57	17.16%
4	Metformin	49	14.75%
5	Budesonide	29	8.73%

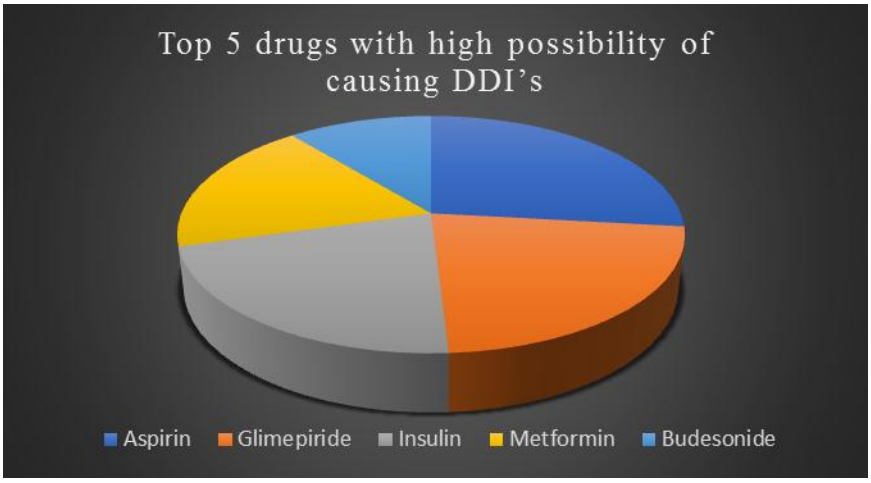

Fig. 4: Top 5 drugs with high possibility of causing DDI's.

DISCUSSION

Among the surveyed 100 prescription it was observed that 53% were men and 47 % were women showing that men predominated women. The result was seen similar to the study conducted by G Ramachandran.[13], Diabetes mellitus was more common in the age group of 59-78 with 43% of the patients, followed by age group of 39-58 with 34% of the Patients, which is followed by the age group 18-38 with 16. Patients above 79 were 7%. 58% of the patients were 50 years of age or more had diabetes mellitus which is also stated in research conducted by G Ramachandran and David N *et al.* [13][14] Age group 18-38 should be focused since 16% of the diabetic patients belong to this category or age groups this may be because of the lifestyle, stress etc they are facing was mentioned in research was conducted by Manjusha S *et al.*,[4]

53 patients who were having diabetes were also having hypertension the finding was similar to the study conducted by Arauz-Pacheco *et al.* [18] and 32 patients were prone to gastritis problem.[19] 16 patients were having cardiovascular disease this finding was similar to the research conducted by SC Smith Jr *et al.*,[19] 15 patients had edema, 11 patients had neurological disorder 10 were having asthma and patients with other diseases were 103.

This study has the results of patients having hypertension disease along with diabetes as per the study conducted by Araurz -Pacheco C *et al.*,[18] which states that around 20-60% of the diabetic patients also have hypertension. It was noticed that the Insulin had interaction with antihypertensive drugs in 10 prescriptions this reduce the insulin sensitivity and the catabolism of insulin will also decrease.

Gastritis medications can also influence the risk in terms of diabetic patients.

Regarding the use of statins for lowering the cholesterol level it was observed that statins increased the risk of diabetes mellitus.[25]

The common interactions between 2 anti-diabetic agents

Hormonal anti-diabetic drugs were found to be interacting with other anti-diabetic class of drugs such as sulfonylurea, biguanides, DDP-4 8,7 & 1 prescriptions which were moderate interactions respectively. Insulin with some of the sulfonylurea drugs such as glimepiride can increase the effective metabolic control with reduced incidence of nocturnal hypoglycaemia [26]. Also insulin with metformin gives a synergistic effect although metformin alone generally does not cause hypoglycaemia under normal circumstances of use, the added therapeutic effect when combined with other anti-diabetic agent may result in hypoglycaemia [27]. 5 drugs that were seen to be having interactions in most number of times were Aspirin was seen having interactions 71 times (21.38%). Glimepiride had interactions 59 times (17.77%). Insulin had interactions 57 times (17.16%). Metformin and Budesonide were seen having interactions 49 (14.75%) & 29 (8.73%) respectively.

Insulin with most of the other anti-diabetic drugs have shown the hypoglycaemic effects.

Sulfonylurea was seen to be interacting with biguanides and DDP-4 most of the effects were synergistic effects. It was noticed that 12 prescriptions had interactions between metformin and sulfonylurea Gottschalk *et al.,* [23]. Sulfonylurea along with DDP-4 also show synergistic

effects it is also mentioned in Safety and efficacy of sitagliptin compared with glimepiride in patients with type 2 diabetes mellitus inadequately controlled with metformin monotherapy.

Interactions between anti-diabetic drugs and other drugs accounting for higher threat of DDI's

The most common interacting pairs of drugs that are found to be between aspirin and clopidogrel in 9 patients, metformin and glimepiride in 11 patients, aspirin and insulin in 10 patients, insulin and metformin in 6 patients, aspirin and glimepiride in 14 patients and telmisartan and aspirin in 14 patients.

Aspirin irreversibly acetylate cyclooxygenase (cox)-1 enzyme which in turn supresses thromboxane A_2. Clinical cause of aspirin resistance can result in clinical factors such as non-compliance, non-absorption, acute coronary syndrome, CHF, hyperglycaemia etc. Cellular factors such as increased norepinephrine, erythrocyte induced platelet activation can be seen. Genetic factors like collagen receptor polymorphism can be noticed.[31]

Metformin and glimepiride, insulin and metformin can give synergistic effect hence the DDI need to be a area of concern.[32]

Aspirin along with insulin may increase the risk of hypoglycaemia or low blood sugar level. Insulin resistance was an independent risk factor for antiplatelet drug resistance in patients with stroke.[33]

Aspirin with glimepiride increase the risk of hypoglycaemia. Aspirin and telmisartan if taken together then the combination act as antagonist for telmisartan and reduce the effect of telmisartan in reducing the blood pressure.[34]

The most common drug that was found to be influencing the DDI was aspirin which was seen to be interacting telmisartan, glimepiride and amlodipine in 53 patients and also aspirin have interacted with other drugs but not as many times as the drugs mentioned above. Aspirin may decrease the effect of the drugs.[35]

Other drugs that influenced in the probable DDI were glimepiride, metformin, furosemide. Interactions between 2 anti-diabetic drugs play a synergistic role. Interaction between furosemide and metformin observed that furosemide increased the effect of metformin but metformin decreased the effect of furosemide.[36]

CONCLUSION

Our study helped to grasp about the most likely prone age group, disease circumstance and common mechanism that can cause drug-drug interactions in inpatient prescription. This in addition had assisted in enhancing protection & effective use of medicines in hospital.

The use of drug interaction checker software had extensively helped our study by using assessing the discovering cited above greater easily, this would have been tougher task to achieve if achieved manually. Our project also helped to define the considerable role of pharmacist in assessing and controlling drug-drug interactions.

It was observed that the patients taking insulin, glimepiride, metformin, sitagliptin etc anti-diabetic drugs had interactions with other drugs such as ranitidine, tramadol, pantoprazole, telmisartan, atorvastatin, clonidine, furosemide, budesonide etc were associated with disease such as gastritis, hypertension, heart related problems, asthma, arthritis etc.

Interactions between 2 anti-diabetic drugs were showing synergistic effects,
The most common interacting pair of drugs were aspirin – glimepiride and aspirin – telmisartan.
Insulin with sulfonylurea and sulfonylurea with biguanides were the anti-diabetic classes that had interactions in more numbers between 2 anti-diabetics therapeutic classes.

The most probable interactions were between aspirin and telmisartan, glimepiride and insulin. Poly-pharmacy must be a region/sector of serious problem in diabetes mellitus, specially in the elderly patients. In our study diabetes patients received more drugs.Strategies to minimize prescription of needless medicinal drug are appreciated and could enhance high-quality existence and adherence to remedy in patient with diabetes.

LIMITATION

- Duration of study was of limited period.
- Since the survey was focused in one particular institution, it is difficult to generalize the findings.
- We considered only the in-patients, the out-patients were excluded from the survey.
- The sample size was restricted to 100.
- Patients below the age of 18 were not considered.

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