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# Possible drug interactions in the management of Metabolic Syndrome

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## ABSTRACT

Metabolic syndrome is treated with multiple drugs leading to high potential of drug interactions. This article is to carry out a review to analyze the potential drug interactions in the management of metabolic syndrome. It focuses on the expected drug interactions as well as the reported studies on the occurrence of the drug interactions. Expected drug interactions for drugs used in metabolic syndrome include hypoglycaemia, hypotension and electrolyte disturbances like hypokalaemia. They may cause hyperglycaemia as well. Some unwanted effects like myopathy are also possible. Literature shows adequate reports of ADRs rather than drug interactions. Hence, it is inferred that drug interactions are rarer. More efforts are also needed to get them reported. Drug interactions are more common in diabetes patients. Metformin –NSAID pair seems to be a common drug interaction. ACE inhibitors, anti diabetic agents, NSAIDs and diuretics are commonly involved in drug interactions. Physicians have to focus on clinically significant drug interactions and ensure such interactions are kept to the minimum levels. Rifampicin – glibenclamide pair and gemfibrozil – pioglitazone pair have caused drug interactions. NSAID – sulfonylurea pair can cause significant hypoglycaemia. Microbe environment can influence the pharmacokinetic aspects of some drugs and hence, caution is required while prescribing drugs like probiotics and antimicrobial agents, though conclusive studies on pharmacomicrobiomics are expected in the future. Caution in the use of multiple drugs and adequate patient education are needed to prevent drug interactions and manage them at the earlier stages.

**Keywords:** - Drug interactions, metabolic syndrome, anti diabetic agents, antihypertensive agents, hypolipidemic agents, antiobesity agents.

## INTRODUCTION

From Metabolic syndrome is very common nowadays. It is otherwise called as “Syndrome X”. In most places, patients are diagnosed as diabetics, hypertensives, hyperlipidemics etc. Full investigations of these patients will show other co-existing abnormal parameters and help one to diagnose them as patients of “Metabolic syndrome”. These patients will usually need multiple drugs for treatment leading to higher chances of drug interactions. This article will review the actual nature of drug interactions possible in these patients.

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Metabolic syndrome is recognized when three or more of the abnormalities out of abdominal obesity, elevated fasting blood glucose level, insulin resistance, hyperlipidaemia and hypertension are present. These patients also show elevated catecholamines and elevated inflammatory markers. They also show higher risk of fatty liver disease. Metabolic syndrome is also seen in association with PCOD [1].

## NON – PHARMACOLOGIC MEASURES ADOPTED FOR TREATMENT OF METABOLIC SYNDROME

Lifestyle modifications and Mediterranean diet are often recommended for patients suffering from metabolic syndrome. These include weight loss measures also. Regular physical activity and stress management are emphasised. Good sleep is emphasised besides "quitting from smoking" [2].

## PHARMACOLOGIC MEASURES ADOPTED FOR THE TREATMENT OF METABOLIC SYNDROME

Medicines are recommended to tackle every component of the metabolic syndrome, as depicted in Table 1.

**Table 1: Medicines recommended in the management of metabolic syndrome**

| Serial number | Medicines recommended |
|---|---|
| 1 | Antihypertensives |
| 2 | Antidiabetic agents |
| 3 | Hypolipidaemic agents |
| 4 | Weight loss medicines |
| 5 | Other medicines for co-morbid conditions |

## DRUG INTERACTIONS EXPECTED IN THE TREATMENT OF METABOLIC SYNDROME

Components of metabolic syndrome are treated individually. Different drugs are prescribed leading to polypharmacy and this, in turn, leading to drug interactions. Commonly expected drug interactions are tabulated below in table 2:

**Table 2: Common drug interactions expected in the treatment of metabolic syndrome** [3]

| Name of the drug | Drug interaction(s) expected |
|---|---|
| Thiazides | Can reduce sulfonylurea action. Can diminish the uricosuric action of probenecid |
| Enalapril , Losartan | Diuretics may precipitate hypotension. Indomethacin attenuates the hypotension action. K sparing diuretics can cause hyperkalaemia. |
| Amlodipine | Positive effect with beta blocker |
| Atenolol | Drug interactions are less as it is a cardioselective beta blocker |
| Insulin | Beta blockers can prolong hypoglycaemia. They can mask the warning signs of hypoglycaemia also. Furosemide and steroids may increase blood sugar level countering the actions of insulin. Theophylline can accentuate hypoglycaemia. |
| Sulfonylureas | Sulfonamides can precipitate hypoglycaemia. Warfarin can precipitate hypoglycaemia. Phenytoin and rifampicin can reduce diabetes control. Corticosteroids, diuretics and oral contraceptives can have opposite action on blood sugar level |
| Vildagliptin | Significant drug interactions are not reported |
| Metformin | Furosemide can enhance the toxicity |
| Pioglitazone | Metabolism induced by rifampicin. Failure of oral contraception can occur |
| Acarbose | Drug interactions not expected |
| Statins | Myopathy and liver injury are more common with gemfibrozil or CYP3A4 inhibitors |
| Fenofibrate | Relatively safer with statins when compared with other fibric acid derivatives |
| Ezetimibe | Drug interactions are not expected |
| Orlistat | Interferes with absorption of vitamins. It may decrease the absorption of oral contraceptives and cyclosporin(4) |

## DRUG INTERACTIONS IN METABOLIC SYNDROME

### Impact of polypharmacy

Drug interactions are expected when one treats metabolic syndrome with multiple drugs. Frequency of drug interactions indicates the quality of prescribing adopted [4]. Many studies are available regarding this aspect. List of common drugs used in metabolic syndrome also varies from country to country. Hence, the need for such studies on adverse drug effects and drug interactions separately in every country. The most common ten drug interactions in obesity patients are enumerated in a study by Emine Nur Ozdamar et al. [5].The most common DDI between drugs prescribed at obesity clinic was found to be metformin – NSAID pair.

### Impact of comorbidities

Comorbidities also influence the frequency of drug interactions. Different studies identify different comorbid conditions as associated with drug interactions. In a study, Ozdamar et al identified diabetes mellitus as the common condition associated with drug interactions [5]. From this, it is imperative that one should be more careful with diabetes mellitus patients as they are more prone to develop drug interactions. Recording and highlighting a large number of drug interactions may lead to" data alert" fatigue among health care providers [6]. Hence, one has to exercise caution while reporting any large number of drug interactions . It is better to concentrate on drug interactions which might cause clinically significant effects**.**

### Reporting status of drug interactions

Published literature is plenty about ADRs but not on drug interactions.Some articles on drug interactions are written when the drugs are launched and they mainly pertain to the pharmacokinetic aspects. Subsequent articles on drug interactions are scarce. This might be due to lower incidence of drug interactions .Drug interactions may also be getting published as case reports in the concerned speciality journals.

### Drug interactions involving ACE inhibitors

In a pharmacokinetic " in – vitro" study by Naveed S and Sadia H (2021), it was found that captopril and lisinopril levels were affected by antidiabetic drugs [7]. Captopril – aspirin interaction was found as the most common interaction in a study by Santi Purna Sari et al. [8]. This article is an extensive review of drug interactions involving ACE inhibitors.

In another article by Andre J Scheen, it is highlighted that most of antidiabetic agents don't cause significant drug interactions except those involved in the metabolism by cytochrome enzymes. It also highlighted that some antihypertensive agents like ACE inhibitors would increase chances of hypoglycaemic episodes when given with regular antidiabetic agents. One has to go by specific case

reports of drug interactions rather than by elaborate, planned studies given the rarity of occurrence of drug interactions [9].

Drug interactions involving Amlodipine and statins

Shinichiro Nichio et al conducted a study to analyze pharmacokinetic and pharmacodynamic interactions between statins and amlodipine. They found that amlodipine enhanced the level of statins by 30% but opined that that might not lead to significant effect on pharmacodynamic aspects. However, their study had a smaller sample size to detect any pharmacodynamic effect. They conclude that compared with diltiazem, amlodipine is safer in combination with statins [10].

**Studies involving prescription patterns**

In a study by Kiki Rawitri et al, prescriptions of diabetes patients were analyzed for drug interactions. It was concluded that prescribers had better consider the severity of drug interactions before co-prescribing drugs for diabetes [11].

Drug interaction involving glibenclamide and rifampicin

V Surekha et al did a study to analyze the effect of rifampicin on glibenclamide. They found that blood sugar went uncontrolled while adding rifampicin and became normal after discontinuing. With rifampicin, there was a need for dose modification of glibenclamide. After six days of stopping of rifampicin, blood sugar normalized [12].

**Drug interactions involving vildagliptin**

Yan-Ling He studied the pharmacokinetic and pharmacodynamic aspects of vildagliptin. . It was concluded that vildagliptin was safe either alone or with other antidiabetic agents at a dose of 50mg once daily or twice daily [13].

**Drug interactions involving metformin**

Naina Mohamed Pakkir Maideen et al have published an elaborate paper on drug interactions involving metformin. Pharmacokinetics of metformin depends on Organic Cation Transporters (OCTs), Multidrug and Toxin Extruders (MATES) and Plasma membrane Monoamine Transporter (PMAT). Drugs such as Cimetidine, Ranitidine, Proton Pump Inhibitors (PPIs), Trimethoprim, Cephalexin, Dolutegravir, Pyrimethamine, Ranolazine, Vandetanib, and Atenolol inhibit either OCTs or or MATES both leading to decreased elimination and increased exposure of Metformin leading to metformin toxicity which can cause lactic acidosis [14].

Prasarn Manitpisitkul et al in their article highlighted the drug interaction possibility between metformin and topiramate. Though clinically significant drug interaction was not noted in healthy volunteers, caution is warranted when prescribing them together [15].

**Drug interactions involving pioglitazone**

A descriptive article by André J Scheen highlighted that gemfibrozil caused a rise in AUC of pioglitazone. Hence, suitable dose reduction of pioglitazone is needed when gemfibrozil is co-prescribed [16].

**Drug interactions involving acarbose**

In his review article, Naina Mohamed Pakkir Maideen highlights that Acarbose group of drugs are safer with other antidiabetic agents, in fact aiding the glucose control effects of other drugs [17].

**Drug interactions involving ezitimibe**

Teddy Kosoglou et al, in their review article, mention that ezetimibe is safer with many drugs without causing drug interactions. They recommend that cholestyramine and ezetimibe must be taken hours apart to avoid attenuating efficacy of ezetimibe. They also recommend that physicians take more caution when prescribing ezetimibe with cyclosporine. It is better to monitor cyclosporine levels in such situations [18].

Chang Hee Kim et al confirm the safety of the combination of rosuvastatin and ezetimibe. They did a study as original research article, a cross over trial involving healthy male subjects. They noticed no adverse drug effects due to this combination [19].

**Drug interactions involving hypolipidemic drugs**

Hae Won Lee et al , in their pharmacokinetic study on fenofibrate and pitavastatin found no pharmacokinetic effects due to drug interaction [20].

**Drug interactions involving orlistat**

Theodosios D. Filippatos et al, in their article, highlighted that orlistat interferes with absorption of many drugs including fat soluble vitamins [21].

Agam B. Bansal; Preeti Patel; Yasir Al Khalili. emphasize that antiepileptic agents needs monitoring when orlistat is given along with them [22].

**CURRENT STATUS ON THE DRUG INTERACTIONS BASED ON THE AVAILABLE LITERATURE**

Review of literature shows the adequate availability of information about ADRs in the treatment of metabolic syndrome while information on drug interactions is found less only. This shows good safety profile of polypharmacy adopted in this clinical situation unlike other clinical situations.

Possilibity of drug interactions should be considered for diabetes mellitus patients as they can undergo fluctuations in blood sugar levels. Moreover, steps can be taken to encourage health professionals to report drug interactions as part of pharmacovigilance program.

When comorbidities are present, care givers add more drugs. For ex Rifampicin in pulmonary tuberculosis . Such drugs can cause drug interactions leading to fluctuations in blood sugar levels. When more drugs are added to patients taking metformin, glibenclamide and pioglitazone, one has to be more

careful and one should take more precautions like patient education regarding ADR recognition and prompt ADR management by the first contact health professionals.

It is needless to say that NSAIDs can cause displacement of sulfonylureas causing hypoglycaemia [3]. It is better to avoid concurrent use of NSAIDs or substitute NSAIDs with paracetamol. It is better to educate patients about recognizing and managing impending hypoglycaemia. Dispensing pharmacists can also look for potential drug interactions by using drug interaction checkers available online, especially for patients taking multiple drugs. Physicians have to follow up the patients with prompt recording of any deviation in laboratory values and new changes in the patients" clinical condition so that they could identify the drug interactions at the earliest stage and take remedial measures.

Similar precaution is warranted in diabetics when they are put on diuretics for comorbid conditions. Similar caution is needed in patients taking ezetimibe when cyclosporine and cholestyramine are added for other clinical indications. Similarly, caution is needed with patients taking orlistat, as one has to look for vitamin deficiencies. Such patients, when put on antiepileptic drugs also need close monitoring.

**Upcoming role of Pharmacomicrobiomics**

Variability of drug response to ACE inhibitors, Sitagliptin and Vildagliptin can also be due to microbiomics [23]. Hence, coprescription of antimicrobial agents with these drugs may need close monitoring for drug interactions. Such steps can lead to better therapy with less ADRs and less drug interactions enhancing patient safety besides aiding the development of personalized medicine in future.

**Drug interactions involving metformin and cimetidine**

In his pharmacy update article by Curtis Triplitt, pharmd, CDE, importance of cimetidine elevating metformin levels , through competing with renal excretion is highlighted. This article also discusses, in an elaborate way, the mechanism of drug interactions of various antidiabetic drugs, besides discussing disease-drug interactions [24].

## CONCLUSIONS

Review of literature was carried out to know the incidence of drug interactions in the management of metabolic syndrome. More ADRs were encountered and less number of drug interactions was noted. This should prompt one to enhance "drug interaction reporting"among health care providers .Special care has to be given in diabetics and hypertensives when more drugs are added for other components of metabolic syndrome or for comorbidities. In this context, patient education about ADRs, early warning signs and management of ADRs and drug interactions are to be kept in mind. Possible drug interactions as outlined above are also to be kept in mind. When comorbidities occur warranting multidrug therapy or when chronic medications are prescribed as in tuberculosis, epilepsy and organ transplantation, one has to actively look for drug interactions during the follow up visits.

Coprescription of antimicrobial agents can lead to pharmacokinetic alterations leading on to significant clinical disturbances like hypoglycaemia and hypotension. Hence, pharmacomicrobiomics aspect also has to be kept in mind when one manages metabolic syndrome.

In this context, it will not be out place to highlight that ADR like events and Drug –interaction like events can occur not only due to coprescribed drugs and comorbid conditions but also due to frequent changes in regular drugs, changes in fixed dose combinations prescribed, supply of alternatives in the pharmacy counter and last , but not the least, . confusion in the mind of patients due to these factors. Patient's age and memory level also will contribute to such events besides medication errors and non-compliance or overcompliance. So, health care providers have to consider all these things during prescribing and during follow up visits of metabolic syndrome patients. These steps will reduce drug interactions, enhance patient safety, reduce unnecessary admissions as in- patients leading to minimization of treatment cost and improved patient compliance.

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