Assessment of pharmacotherapy pattern in metabolic syndrome

Anum Sultana[1], V Preethi Sharon[1], Venkatesh Prasanna[1]*, NK Meera[2], Pavankumar P Rasalkar[3].

[1] Doctor of Pharmacy, Department of Pharmacy Practice,
Visveswarapura Institute of Pharmaceutical Sciences, Bengaluru, Karnataka, India 560070

[2] Head of Department, Professor, Department of Pharmacy Practice,
Visveswarapura Institute of Pharmaceutical Sciences, Bengaluru, Karnataka, India 560070

[3] Head of Department, Associate Professor, Department of Cardiology,
KIMS Heart Centre, KIMS Hospital and Research Centre, Bengaluru, Karnataka, India 560004

***Corresponding author:** E-mail ID: prasannad1729@gmail.com
Telephone no.: 9535972557

ABSTRACT: BACKGROUND: According to International diabetes federation (IDF), Metabolic Syndrome (MetS) is a cluster of the most dangerous cardio vascular risk factors of abdominal obesity, elevated blood glucose level, elevated blood pressure and dyslipidemia. PURPOSE: The main objective of this study was to assess the pharmacotherapy management and also to identify and report any drug-drug interactions from the treatment charts. MATERIALS AND METHOD: A 6 months prospective study was carried out in 156 patients of either gender between the age group 18 to 70 years attending the cardiology department of a tertiary care hospital. The demographic, diagnosis, pharmacotherapy data were documented and analyzed for pharmacotherapy pattern and drug-drug interactions. RESULTS AND DISCUSSION: The occurrence of MetS was higher in males (61.54%) than in females (38.46%). The maximum number of patients were between the age group 51 to 70 years. The anthropometric values (waist circumference, height, weight and BMI) were comparatively higher in males than in females whereas clinical parameters (systolic, diastolic blood pressure, fasting blood glucose, serum triglycerides and HDL) showed no significant differences between the genders. Pharmacotherapy assessment showed prescribing of anti-hypertensives greater than anti-diabetics and anti-dyslipidemics. Most of the drug interactions assessed were potential, moderate in severity, 46.56% and 41.3% from risk categories B and C respectively. CONCLUSION: A rational, systematic approach of pharmacotherapy of morbid conditions is most essential in management of patients with MetS for their overall health related quality of life.

KEY WORDS: Cardiovascular disease (CVD), International diabetes federation (IDF), metabolic syndrome (MetS), pharmacotherapy.

1. INTRODUCTION:

According to International diabetes federation (IDF) - Metabolic Syndrome (MetS) also known as Syndrome X, is a cluster of the most dangerous cardio vascular risk factors which includes abdominal obesity, elevated blood glucose level, elevated blood pressure, dyslipidemia.[1] The two basic reasons leading to the increased prevalence of metabolic syndrome are:

1. Increase in consumption of high calorie – low fiber fast food.

2. Decrease in physical activity and increase in sedentary life style.

Metabolic syndrome is about three times more common than diabetes, the global prevalence is estimated to be about one quarter of the world population. In other words, worldwide an estimated billion people are currently diagnosed with metabolic syndrome.[2]

The diagnostic criteria for the metabolic syndrome include central obesity (defined as waist circumference ≥94 cm in men or ≥80 cm in women) together with any two of the following: fasting plasma glucose (defined as glucose level ≥110 mg/dL) or previous diagnosis of diabetes, blood pressure of 130/85 mm Hg or higher and triglyceride level of 150 mg/dL or higher, low HDL-C level (defined as < 40 mg/dL in men or < 50 mg/dL in women).[3]

The primary goal in the management of metabolic syndrome is to modify the underlying risk factors (obesity, physical inactivity, and atherogenic diet) through lifestyle changes. Diet, physical activity, sleep, emotion control, peer support, and avoidance of tobacco, alcohol, and other drugs/ medications that alter body weight are key targets of any healthy lifestyle program.[4]

MANAGEMENT OF INDIVIDUAL COMPONENTS OF METABOLIC SYNDROME:

Elevated fasting glucose: In the metabolic syndrome diagnosis, elevated fasting glucose (≥110mg/dl) includes both IFG (impaired fasting glucose) and type 2 diabetes mellitus. The goals of managing elevated fasting glucose are – to lower fasting glucose in patients with IFG to delay the onset of type 2 diabetes mellitus and to intensively manage type 2 diabetes mellitus using insulin and oral hypoglycemic agents. Metformin, thiazolidinediones and acarbose lower risk of type 2 diabetes mellitus in patients with IFG.[5]

Elevated blood pressure: For patients who require blood pressure reduction for general heart disease prevention, or for patients at high risk of the development of coronary artery disease, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), calcium channel blockers, and thiazide type diuretics are all appropriate as first-line therapy or in combination as necessary.[6] Therapy with beta-blockers can be added to these antihypertensive classes but is primarily used in patients with stable angina, myocardial infarction, or left ventricular systolic dysfunction.[7]

Atherogenic dyslipidemia: Apart from lifestyle modification, drug therapy is also considered in patients with atherogenic dylipidemia. Lipid lowering therapy majorly targets LDL cholesterol levels. Statins are usually the first choice of drug which reduces apolipoprotein B-containing lipoproteins. Triglyceride lowering drugs like fibrates and nicotinic acid reduce triglycerides, small LDL particles, non HDL-C; raises HDL-C and reduce risk for atherosclerotic cardiovascular disease (ASCVD).[8, 9]

Since managing individual component of MetS is important so as to prevent the progression of further complications like CVD, stroke etc, this study was carried out for the assessment of pharmacotherapy pattern and drug- drug interactions as the objectives of the study.

2. MATERIALS AND METHOD:

A 6 month prospective observational study was conducted in the cardiology department of a tertiary care teaching hospital in Bangalore, India after approval from Institutional Ethics Committee with a sample size of 156 patients who participated on voluntary basis by giving their consent. Inpatients and outpatients of either gender diagnosed with metabolic syndrome in the age group of 18 -70 years were included. Patients with chronic renal, hepatic diseases, chronic obstructive pulmonary disease, psychiatric condition, polycystic ovary syndrome diagnosed, terminal illnesses were excluded.

During the study, patients' case sheets were reviewed and consenting patients were interviewed personally for the collection of data which were recorded in self designed data collection form. Data like demographic details, presenting complaints, past medical and medication history, family and social history, anthropometric data, clinical parameters, details on pharmacotherapy were obtained. The case sheets were assessed for drug-drug interactions using databases like Lexicomp, Stockleys drug interaction with respect to mechanism, severity and risk rating.

ANALYSIS OF DATA: Descriptive statistics in terms of number and percentage was used to assess the demographic data and pharmacotherapy pattern of drugs, the quantitative parameters of anthropometric data and laboratory measurements were assessed and reported in terms of Mean ± SD, and the results are presented at 5% level of significance.

3. RESULTS:

On classification into IP and OP, out of 156 patients, 61.54% were outpatients and 38.46% were inpatients. Out of 96 outpatients, 36.46% subjects were female and 63.54% were male. Out of 60 inpatients, 41.67% subjects were female and 58.33% were male. Majority of the patients had lower level of education and no occupation.

Current diagnosis of the patients showed that, 32.26% patients had Type 2 DM, 34.37% had hypertension, 7.58% had dyslipidemia and 20.08% had IHD. 78% patients had both DM and hypertension whereas only 12.8% patients had Type 2 DM, hypertension and Dyslipidemia. 47.98% had past medical history of DM and 48.99% had hypertension, almost all patients had past medication history and were taking anti-diabetic and anti-hypertensive drugs respectively.

In our study 73.72% patients were found to have no habits of addiction like smoking, drinking alcohol, chewing tobacco, drug abuse, etc., indicating higher awareness about the ill effects of such habits. The diagnosis of patients was based on IDF criteria, Table I summarizes the parameters of age, gender as well as IDF criteria parameters in terms of mean ± SD.

Table I: Mean ± SD of Age and IDF criteria parameters between genders.

Parameters	Female (n= 60)		Male (n= 96)		*P*
	Mean ± SD	Range/ value	Mean ± SD	Range/ value	
Age (years)	59.6 ± 8.67	18-70	58.85 ± 9.00	18-70	0.41
WC (cm)	100.68 ± 9.23	≥80	101.61 ± 9.47	≥94	0.58
FBS (mg/dl)	147.21 ± 40.78	≥ 110	151.64 ± 42.09	≥ 110	0.52
SBP (mmHg)	147.78 ± 23.81	≥130	144.04 ± 19.7	≥130	0.31
DBP (mmHg)	89.65 ± 10.02	≥85	88.85 ± 11.26	≥85	0.64
TG (mg/dl)	203.16 ± 37.42	≥150	235.17 ± 114.04	≥150	0.18
HDL (mg/dl)	35.3 ± 8.2	≤ 50	28.85 ± 8.5	≤40	0.01

n= number, SD= standard deviation, *P*= Probability value (P < 0.01) at 5% level of significance, WC= waist circumference, FBS= fasting blood glucose, SBP= systolic blood pressure, DBP= diastolic blood pressure, TG= triglycerides, HDL= high density lipoprotein.

The overall pharmacotherapy assessment showed that the prescribing of anti-hypertensives was greater than anti-diabetics or anti-dyslipidemics in both IP and OP whereas the prescribing of other drugs like anti-platelets aggregating agents, anti-coagulants, nitro vasodilators, antibiotics and PPI were found to be greater in IP rather than OP. (Table II)

Table II: Pharmacotherapy pattern.

CLASS OF DRUG		OP		IP	
		N	%	N	%
Anti-Diabetics		101	22.39	69	17.83
Anti-Hypertensives		161	35.7	120	31.01
Anti-Dyslipidemics		91	20.18	59	15.25
OTHERS	Anti-Platelet aggregating agents	50	11.09	42	10.85
	Anti-Coagulants	1	0.22	8	2.07
	Nitro vasodilators	19	4.21	18	4.65
	Antibiotics	5	1.11	40	10.34
	PPI's	23	5.1	31	8.01

N= frequency of drug usage, OP= outpatient, IP= inpatient, PPI's= proton pump inhibitors.

145 patients were diabetic and the total frequency of prescribing of antidiabetic drugs were 101 in OP and 69 in IP. The drugs were administered as either monotherapy or in combination. The most commonly used drug in monotherapy was insulin (22.77% in OP and 69.57 % in IP) whereas in combination therapy, Glimepiride and metformin (43.56 % in OP and 15.94% in IP) was the preferred and most commonly used drugs in two drug combination while glimepiride, metformin and voglibose (9.90 % in OP and 4.35% in IP) were the preferred drugs in three drug combination.

154 patients were hypertensive and the total frequency of prescribing of antihypertensive drugs were 161 in OP and 120 in IP. The most commonly used drugs in monotherapy were metoprolol (25.47 % in OP and 16.67 % in IP), furosemide (4.97% in OP and 30 % in IP) and telmisartan (14.29% in OP and 8.33% in IP) whereas in combination therapy, torsemide and spironolactone (14.91% in OP and 5% in IP) and telmisartan and metoprolol (8.70% in OP and 3.33% in IP) were the preferred and most commonly used drugs in two drug combination whereas telmisartan, amlodipine and hydrochlorothiazide (1.86% in OP and 2.50% in IP) was the only three drug combination used.

34 patients were dyslipidemics and the total frequency of prescribing of antidyslipidemic drugs were 91 in OP and 59 in IP. The most commonly used drugs in monotherapy was atorvastatin (19.78% in OP and 30.51% in IP) and rosuvastatin (19.78% in OP and 20.34 % in IP) whereas in combination therapy, anti dyslipidemic drug was given along with anti-platelet aggregating drug, which included atorvastatin with aspirin (15.38% in OP and 11.86% in IP) in two drug combination and rosuvastatin with aspirin and clopidogrel (28.57% in OP and 22.03% in IP) in three drug combination.

The pharmacotherapy was assessed for drug-drug interactions and 288 potential interactions were observed. The drug interactions were classified based on the severity as major (24 interactions), moderate (220 interactions) and minor (44 interactions) (Fig. I) which were either pharmacodynamic or pharmacokinetic in nature. Risk rating of the drug interactions were assessed using lexicomp and is summarized in Table III.

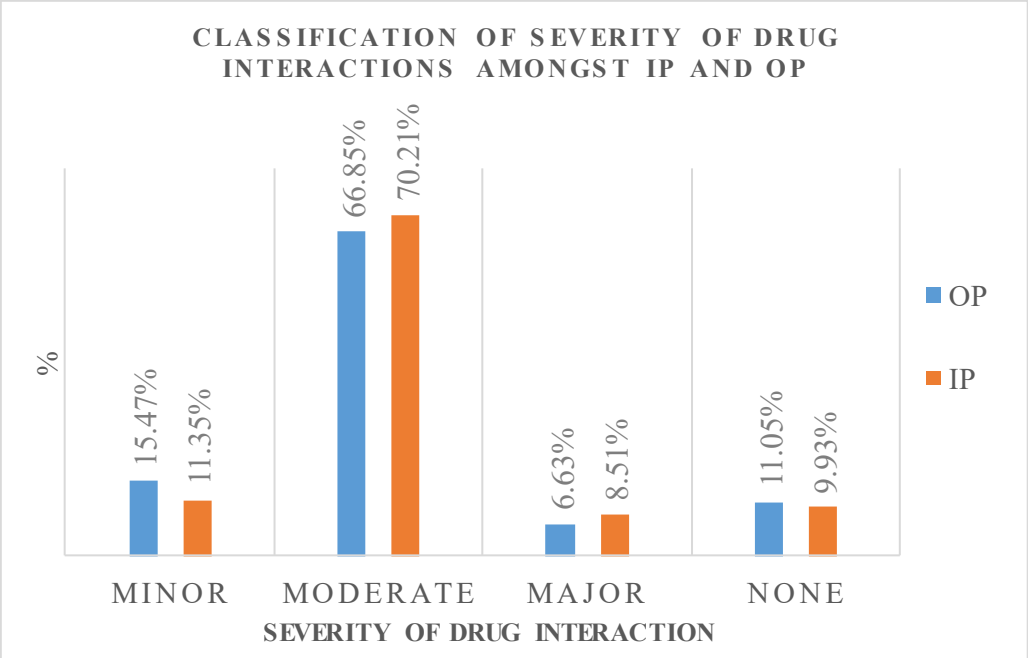

Figure 1: Classification of severity of drug interactions amongst IP and OP.

= OP, Outpatients.

= IP, Inpatients.

X axis: Severity of interaction (Minor, Moderate, Major and None).

Y axis: Percentage (%) of drug interactions.

Table III: Risk rating categories of drug interactions.

Risk rating	Action taken	N
A	No interaction	34
B	No action needed	150
C	Monitor therapy	133
D	Modify regimen	5
X	Avoid combination	0

4. DISCUSSION:

Each component of MetS is an individual risk factor for occurrence of CVD (IHD, MI, stroke etc), hence it becomes necessary to assess the appropriateness of pharmacotherapy of these individual components of MetS.

Comparing both IP and OP, it was found that the occurrence of the metabolic syndrome is greater in male 61.54% than in female 38.46% subjects. A similar study which analyzed prevalence of MetS in Urban India by Sawant A et al. showed that prevalence of MetS in males was higher than female, whereas in other studies in India, MetS prevalence was found to be higher in female than in males.[10]

We observed that, nearly half of the total sample population were between the age group 61 to 70 years and as age increased the number of patients with MetS also increased. Swastika K et al. found significantly higher prevalence of MetS in the elderly group (≥60 years) than the younger age group (<60 years).[11]

Patient's knowledge, education level and active lifestyle play a large role in preventing and managing the components of MetS. It was found that majority of patients with MetS had a lower education level.

It was found that almost all patients had DM and Hypertension as they are the major contributors of MetS. The presence of DM and hypertension was found to be higher in patients aged between 51 to 70 years. More than half of the study population was diagnosed with IHD as a result of complication of MetS. 91.25 % of the study population either had no family history or failed to report due to lack of recall. Only 10 out of 156 patients have reported a family history of DM and hypertension.

A study by Slagter N S et al. stated that heavy alcohol consumption and moderate to heavy smokers had a higher prevalence of MetS, regardless of the amount of alcohol consumed. Smoking and alcohol consumption further worsens MetS and plays a role as major risk factor for cardiovascular events.[12] In our study 73.72% patients were found to have no habits of addiction.

The IDF criteria parameters showed no significant differences between males and females. A similar study by Sharma R et al. which aimed to determine the prevalence of MetS using two different criteria (IDF add NCEP-ATP III) showed no significant differences of clinical parameter between males and females.[13]

Pharmacotherapy assessment showed the prescribing of antihypertensives greater than anti diabetics or anti dyslipidemics in both IP and OP whereas the prescribing of other drugs like anti-platelet aggregating agents, anti-coagulants, nitro vasodilators, antibiotics and PPI were found to be greater in IP rather than OP.

According to therapeutic approach for individual component of MetS by IDF, the first line therapy for insulin resistance and hyperglycemia is insulin and metformin whereas acarbose is the drug of choice used to delay the development of T2DM in people with impaired glucose tolerance.[1] The therapy used in the management of diabetes in our study was according to IDF management guidelines. Choice of anti-hypertensives were according to the IDF guidelines, as use of beta blockers was higher as it is primarily used in patients with cardiovascular risks like stable angina, myocardial infarction, IHD and left ventricular systolic dysfunction.[8]

Anti-dyslipidemic drugs like atorvastatin, rosuvastatin were given for patients with dyslipidemia whereas for patients with CVD, anti- dyslipidemics were given in combination with anti-platelet aggregating agents like aspirin, clopidegrel.

The drug interactions in the treatment chart were assessed and 288 potential interactions were found, out of which 263 were pharmacodynamic and 25 were pharmacokinetic in nature. The major interacting drugs were aspirin with enoxaparin, spironolactone with telmisartan, propranolol with clonidine. Most of the moderate drug interactions were caused by aspirin with insulin, glimepiride, metoprolol, telmisartan and unfractioned heparin.

46.58% of the interactions were falling under risk rating category B, which did not require any action and they were minor in severity.

41.30% of the interactions were under risk rating category C which required therapy monitoring, in which most of them were moderate in severity. Ex- Concomitant use of anti-diabetic drugs like insulin, glimepiride along with torsemide results in hyperglycemia. Since torsemide is a hyperglycemia-associated agent, it diminishes the therapeutic effect of insulin and glimepiride. Thus, monitoring of blood glucose levels frequently becomes necessary. Though few interactions were major in severity, they required only therapy monitoring. For example, routine combined use of an angiotensin II blockers like telmisartan with aldosterone antagonist such as spironolactone can lead to clinically important hyperkalemia as telmisartan may enhance the hyperkalemic effect of potassium sparing diuretics and therefore extra caution is to be taken in patients who have other potential risk factors for hyperkalemia such as decreased renal function and diabetes. Concomitant use of aspirin with enoxaparin increases the risk of bleeding and this can be managed by closely monitoring the CBC, PTT, INR levels.

Only 1.55% of the drug interactions had risk rating category D which required therapy modification and were major in severity. Alpha 2- agonists like clonidine may enhance the AV- blocking effect of beta-blockers like propranolol. Sinus node dysfunction may also be enhanced. Beta blockers may enhance the rebound hypertensive effect of clonidine. This effect may occur when clonidine is abruptly withdrawn. This can be managed by withdrawing the beta blocker several days before clonidine is gradually withdrawn. Non selective beta blockers have a greater risk, so cardio selective beta blocker like metoprolol is preferred in therapy modification. Another scenario which required therapy modification was in case of amiodarone with ondansetron. Amiodarone may enhance the QT prolonging effect of ondansetron when given intravenously resulting in arrhythmia and potentially life threatening toxicities. The management included withdrawing ondansetron from the treatment regimen or switching to an alternative anti-emetic like domperidone.

5. CONCLUSION:

Prevalence of metabolic syndrome has become epidemic in proportion with multifactorial contributions. The pharmacotherapy of individual morbid conditions needs to be optimal and rational for overall quality of life of the patients, by following widely accepted guidelines in the management of metabolic syndrome.

6. ACKNOWLEDGMENT:

Authors are greatly thankful to all the study subjects for consenting to participate voluntarily and for their support and cooperation in helping us to carry out our study.

REFERENCES:

[1] The IDF consensus worldwide definition of the Metabolic Syndrome. 2006.
[2] M. G. Saklayen. The global epidemic of the metabolic syndrome. Curr Hypertens Rep. 2018, 20(12): 1-8.
[3] O. Onesi, E. Ignatius. Metabolic syndrome: Performance of five different diagnostic criterias. Indian Journal of Endocrinology and Metabolism. 2014, 18(4): 496-501.
[4] C.A. Aguilar-Salinas and T. Viveros-Ruiz. Recent advances in managing/understanding the metabolic syndrome [version 1; peer review: 3 approved]. F1000Research 2019, 8(F1000 Faculty Rev):370.
[5] B. A. Franklin, J. K. Kahn, N. F. Gordon, et al. A cardioprotective "polypill"? Independent and additive benefits of lifestyle modification. Am J Cardiol. 2004, 94: 162–166.
[6] C. L. Aquilante, J. P. Vande Grind. Metabolic syndrome. Pharmacotherapy selfassessment program, 6th edition: 109-127
[7] S. M. Grundy, B. Hansen, S. C. Smith, et al. Clinical management of metabolic syndrome (2004). AHA/NHLBI/ADA Conference proceedings; 109:551-556.
[8] S. M. Grundy, J. I. Cleeman, S. R. Daniels, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement [published correction appears in Circulation. 2005 Oct 25;112(17):e297] [published correction appears in Circulation. 2005 Oct 25;112(17):e298]. Circulation. 2005, 112(17):2735–2752.
[9] R. M. Krauss, R. H. Eckel, B. Howard, et al. AHA Dietary Guidelines: revision 2000: a statement for healthcare professionals from the Nutrition Committee of the American Heart Association. Circulation. 2000, 102: 2284–229.
[10] A. Sawant, R. Mankeshwar, S. Shah, et al. Prevalence of Metabolic Syndrome in urban India. Hindawi Publishing Corperation 2011. Article ID: 920983.
[11] K. Suastika, P. Dwipayana, M. R. Saraswati, et al. Relationship between age and metabolic disorders in the population of Bali. Journal of Clinical Gerontology and Geriatrics 2. 2011, 47-52.
[12] N. S. Slagter, J. V. Ospaptchuk, J. M. Vonk, et al. Combined effects of Smoking and Alcohol on Metabolic Syndrome. The Lifelines Cohort Study. PLOS ONE. 2014, 9(4).
[13] R. Sharma, R. Sharma, A. Kumar. Metabolic Syndrome: Prevalence (IDF and NCEP-ATP III) in Udhampur, Jammu city. IJPSR. 2019, 10(3):1420-1425.