A PROSPECTIVE COMPARATIVE STUDY OF EFFECT OF TELMISARTAN PLUS DIET AND EXERCISE VERSUS TELMISARTAN AND METFORMIN ON METABOLIC PARAMETERS IN HYPERTENSIVE PATIENTS WITH THE METABOLIC SYNDROME

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ABSTRACT

BACKGROUND
Metabolic syndrome is a group of disorders characterised by hyperglycaemia, central obesity and hypertension and dyslipidaemia. This is a condition which is advocated with increased risk of CVD and diabetes mellitus. It is a major modifiable condition that can be prevented and premature death can be decreased.

MATERIALS AND METHODS
Present study is designed to study the defect of telmisartan with diet and exercise versus telmisartan and metformin on various metabolic parameters in metabolic syndrome patients with hypertension. All the metabolic parameters fasting plasma glucose, insulin (fasting), total cholesterol, LDL-cholesterol, triglyceride, C-peptide Blood pressure, BMI and HOMA-IR were measured at the start of the study and was followed regularly. Final measurements of all these parameters were done after 6 months. Hexokinase method was used for estimation of plasma glucose.

RESULTS
Weight of the patient in group A was decreased from 89.52 yrs. to 79.6 yrs. after 6 months, in group B it was decreased from 86.52 kg to 84.56 kg, similarly body mass index (BMI) was reduced in group A from 30.4 kg/m^2 to 27.5 kg/m^2 and in group B it was reduced from 30.1 kg/m^2 to 29.4 kg/m^2. Fasting plasma glucose was 97.79 mg/dL in group A at the start of the study, after 6 months it reduced to 92.76 mg/dL. In group B the fasting plasma glucose was decreased from 96.86 mg/dL to 89.40 mg/dL. Fasting plasma insulin level has been reduced from 12.21 mIU/L to 10.21 mIU/L in group A and from 12.55 to 9.51 mIU/L in group B. HOMA-IR which was 2.96 in group A was reduced to 2.89 and in group B reduced from 3.03 to 2.82.

CONCLUSION
In our study, we have found that the decrease in weight and body mass index was more in group A than group B percentage change in mean of weight was 12.46% in group A and 4.57% in group B, similarly in BMI was 9.5% and 3.9% respectively. We have found that percentage change in mean of FPG, HbA1C and FPI was more in group B and also the change in HOMA-IR. Before start of the study, basal FPI was more but after six months it decreased, but plasma glucose concentration also decreased that indicates that sensitivity of insulin increased. Diet and exercise has good effect on serum triglyceride and LDL-C, but metformin has good effect on HDL-C and total cholesterol.

KEYWORDS
Metabolic Syndrome, Telmisartan, Metformin.

BACKGROUND
As per the global status report on non-communicable diseases 2014, currently over 80% of cardiovascular deaths occur in low and middle economic country like India and CVD (cardiovascular diseases) are among the top three cause of years of life lost due to premature mortality.[1,2,3] These deaths are preventable, because very cost effective interventions are available to prevent heart disease. Metabolic syndrome is a group of disorder characterised by hyperglycaemia, central obesity and hypertension and dyslipidaemia. This is a condition which is advocated with increased risk of CVD and diabetes mellitus. It is a major modifiable condition that can be prevented and premature death can be decreased.

As per the International Diabetes Foundation (IDF), metabolic syndrome can be defined as central obesity plus any two of the following four factors.[4]

Raised triglyceride	> 150 mg/dL or specificity for this lipid abnormality
Reduced HDL cholesterol	< 40 mg/dL male, < 50 mg/dL female or specificity for this lipid abnormality
Raised fasting blood sugar	FPG > 100 mg/dL or previously diagnosed type-2 DM
Raised blood pressure	SBP > 130 mmHg DBP > 85 mmHg. It is of previously diagnosed hypertension

Various drugs and lifestyle modification has been recommended for the modification of the components of metabolic syndrome. Metformin and telmisartan are two drugs, which have been proved to be effective for treatment of insulin resistance. Both the drugs act by different mechanism of action. Metformin acts by activation of AMP dependent protein kinase (AMPk). The key feature for that is suppress hepatic gluconeogenesis, enhances insulin-mediated glucose uptake and interfere with mitochondrial respiratory chain.[5] Telmisartan, an angiotensin type I receptor blocker has been proved to have additional partial agonistic and selective modulator of PPARY receptor. PPARY acts as a ligand activated transcription factor and mediates improvement of whole-body insulin sensitivity.[6,7]

Diet and exercise is another non-pharmacological way to improve insulin resistance and decrease obesity. Present study is designed to study the defect of telmisartan with diet and exercise versus telmisartan and metformin on various metabolic parameters in metabolic syndrome patient with hypertension.

MATERIALS AND METHODS
This is a prospective, comparative, open labelled randomised study conducted during March 2014 to July 2017 in Department of General Medicine, Konaseema Institute of Medical Sciences, Amalapuram, AP. This study was approved by Institutional Ethics Committee. Before enrolment of the patient for the study, a written informed consent was obtained from patients in predesigned form. Sixty patients were included in this study divided into two groups.

Patients were selected as per inclusion and exclusion criteria.

Inclusion Criteria
Age 20 - 60 yrs.
Body mass index > 26 kg/m2
BP > 140/90 mmHg
TG level - > 150 mg/dL
Exclusion Criteria
- Diabetes and its complications
- Pt. on any other medication
- Pregnancy and lactation
- Hypersensitivity to drug

All the metabolic parameters fasting plasma glucose, insulin (fasting), total cholesterol, LDL-cholesterol, triglyceride, C-peptide Blood pressure, BMI and HOMA-IR were measured at the start of the study and was followed regularly. Final measurements of all these parameters was done after 6 months. Hexokinase method was used for estimation of plasma glucose. For total cholesterol, we used Liebermann-Burchard reaction colorimetric method;

triglyceride was estimated by method of Neri and Fringe. HDL concentration was estimated by precipitation method. LDL concentration was calculated by WHO formula, LDL-cholesterol= total cholesterol– TG/5 – HDL (mg/dL).[7] Plasma insulin was determined by using enzyme-linked immunosorbent assay. HOMA-IR was calculated by using this formula (FPI X FPG)/22.5.[8]

Patients were divided into two groups. Group A were given 40 mg telmisartan and all the guidelines for healthy diet and exercise as per local food habit were explained to them and were followed regularly. Patients were followed regularly. Diet chart given to them were in the range of 1500 kcal and daily activity was in the form of walk of 45 mins with a speed of 5 km/hr, 6 days per week. This activity was followed regularly and personally.

Another group B were given telmisartan 40 mg and metformin 250 mg once daily and general instruction about diet and exercise was given, but there was no individualised approach.

RESULTS
Total sixty patients were included into this study and divided into two groups. Group A belongs to telmisartan group and group B belongs to telmisartan and metformin group. Mean age of the patient in both the groups were comparable to each other, that is 48.19 years and 45.806 years respectively. Weight of the patient in group A was decreased from 89.52 years to 79.6 years after 6 months, in group B it was decreased from 86.52 kg to 84.56 kg, similarly Body Mass Index (BMI) was reduced in group A from 30.4 kg/m^2 to 27.5 kg/m^2 and in group B it was reduced from 30.1 kg/m^2 to 29.4 kg/m^2. Both systolic and diastolic blood pressure was decreased in both the groups. Mean value of systolic blood pressure was decreased to 126.4 mmHg from basal value of 150.95 mmHg. Similarly, in group B mean systolic blood pressure decreased from 149.6 mmHg to 124.6 mmHg. DBP was decreased from 91.52 mmHg to 82.6 mmHg in group A and 96.86 mmHg to 89.40 mmHg in group B.

Fasting plasma glucose was 97.79 mg/dL in group A at the start of the study, after 6 months it reduced to 92.76 mg/dL. In group B the fasting plasma glucose was decreased from 96.86 mg/dL to 89.40 mg/dL. Fasting plasma insulin level has been reduced from 12.21 mIU/L to 10.21 mIU/L in group A and from 12.55 to 9.51 mIU/L in group B. HOMA–IR, which was 2.96 in group A was reduced to 2.89 and in group B reduced from 3.03 to 2.82. Glycosylated haemoglobin was decreased from 6.40 to 6.2 in group A and from 6.56 to 5.8 in group B. In group A, the total LDL-C was decreased from basal value of 136.4 mg/dL to 126.2 mg/dL in group A and similarly from 138.6 mg/dL to 136.2 mg/dL in group B. HDL-C was increased from basal value of 39.6 mg/dL to 41.2 mg/dL in group A and from 40.6 mg/dL to 44.00 in group B. The total cholesterol concentration was

reduced in group A from 206.2 mg/dL to 200.2 mg/dL and group B from 212.2 mg/dL to 190.6 mg/dL. The triglyceride level was reduced to 150.2 mg/dL in group A from basal value of 168.6 mg/dL and in group B basal value of 164.2 mg/dL reduced to 160.2 mg/dL.

Parameters	Group A			Group B		
	Basal (Mean)	After 6 Months (Mean)	% Change in Mean	Basal (Mean)	After 6 Months (Mean)	% Change in Mean
Age	48.19	-	-	45.806	-	-
Weight	89.52	79.6	12.40%	86.52	80.56	4.57%
BMI (kg/m2)	30.4	27.5	9.5%	30.1	28	3.9%
SBP (mmHg)	150.95	126.4	15.89%	149.6	124.6	16.7%
DBP (mmHg)	91.52	82.6	9.9%	92.7	81.6	11.9%
FPG (mg/dL)	97.79	92.76	6.1%	96.86	89.40	8.7%
FPI (mIU/L)	12.21	10.21	16.13%	12.55	9.51	24.2%
HbA1C	6.40	6.2	3.1%	6.56	5.8	10.6%
HOMA-IR	2.96	2.89	2.0%	3.03	2.82	6%
LDL (mg/dL)	136.4	126.2	7.4%	138.6	136.2	1.7%
HDL (mg/dL)	39.6	41.2	4.0%	40.6	44.00	8.86%
Total Chol (mg/dL)	**206.2**	**200.2**	**2.9%**	**212.2**	**190.6**	**5.4%**
TG (mg/dL)	168.6	150.2	10.9%	164.2	160.2	2.4%
Table 1. Change in Metabolic Parameter in Both Groups						

DISCUSSION

In present study, we have evaluated the effect of diet and exercise and telmisartan in comparison with telmisartan with low-dose metformin. In our study, we have found that the decrease in weight and body mass index was more in group A than group B. Percentage change in mean of weight was 12.46% in group A and 4.57% in group B, similarly BMI was 9.5% and 3.9% respectively.

Various studies have been conducted regarding effect of telmisartan and metformin on body weight and BMI. KE Foster Schubernt et al found that diet and exercise is associated with significant reduction in BMI and weight, which is similar to our study.[9] But in the study of Giuseppe Derosa, it is found that telmisartan is associated with decrease in BMI and weight.[10] So in our study, diet and exercise is associated with decrease in BMI and weight which has been done along with oral telmisartan. Decrease in BMI and weight is also found in group B, but it is not as significant as group A. As per the study of Kenyajima et al,[11] low dose metformin is not associated with decrease of BMI and is variable between patient population. So in our study, the effect of addition of metformin to telmisartan is associated with little reduction in BMI and body weight. Decrease in SBP and DBP is similar in groups,[12,13] which is similar to various studies.

In our study we have found that percentage charge in mean of FPG, HbA1C and FPI was more in group B and also the change in HOMA-IR. Before start of the study, basal FPI was more but after six months it decreased, but plasma glucose concentration also decreased that indicates that sensitivity of insulin increased. All these changes were more in group B. The same result was found by Soulmaz Fazdi et al[14] and Marloes P Van Der Aa[15] et al.

Regarding effective addition of metformin to telmisartan on lipid profile, in group A the reduction in LDL-C and TG-C was more but increase in HDL-C was more in group B. The reduction in total cholesterol was more in group B. Mohamed Ali et al found that there is significant reduction in total chol-c and Tg concentration, but decrease in LDL-c is not significant which support our study. Similar result was observed by K. T. Augusti et al and Jenly P Nobes et al.[16,17,18]

CONCLUSION

In this study, we would like to conclude that patients on diet and exercise with telmisartan has good reduction in weight and BMI. The fasting plasma glucose, HbA1C and fasting plasma insulin level used to decrease and there was improvement in insulin resistance, but insulin resistance was better improved in metformin group. Diet and exercise has good effect on serum triglyceride and LDL-c, but metformin has good effect on HDL-c and total cholesterol.

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