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EFFECT OF SGLT-2 INHIBITORS AND METORMIN IN PATIENTS WITH METABOLIC SYNDROME

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Abstract

OBJECTIVES: The World Health Organisation has defined Syndrome X as a pathological state that is distinguished by the presence of abdominal obesity, insulin resistance, hypertension, and hyperlipidemia. Individuals diagnosed with metabolic syndrome exhibit a significantly elevated risk, ranging from two to six times greater, of developing cardiovascular disease and type-2 diabetes in comparison to those who do not present with this condition. The rising incidence of metabolic syndrome has prompted research to primarily focus on evaluating the most appropriate treatment regimen.

METHOD: This study is a prospective, observational analysis of 48 patients with metabolic syndrome who were admitted to a government-run tertiary care hospital. The study collected and analysed information on patient demographics, comorbidities, supportive laboratory and diagnostic parameters, and hospitalisation treatment regimen. Using version 23 of the SPSS software, the correlation between these factors and treatment duration was examined.

RESULTS:

Majority of the patients about 43.75 % of patients fell under the 41-55 age category. There were 50% of the patients receiving metformin and 50% receiving metformin with SGLT-2 inhibitors in which the gender distribution showed higher incidence in females of 56.25% than in males of 43.75% .BMI, FBS, PPBS, HbA1C Blood pressure, TSH, h(CRP), HDL, LDL,TG were each of the variables statistically significant at the 5% level of significance with a 95% confidence interval of 0.

CONCLUSION:

Currently available data highlight the various levels of interaction between metabolic parameters on the clinical efficacy of metformin monotherapy and SGLT-2 inhibitors with metformin add on therapy

Key words: *metabolic syndrome, monotherapy versus combination therapy, metformin, SGLT-2 inhibitors*

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INTRODUCTION:

Metabolic syndrome is a constellation of physiological and biochemical abnormalities characterised by diabetes or elevated fasting glucose levels, central adiposity, abnormal cholesterol and triglyceride (TG) levels, and high blood pressure. India is a major contributor to the global increase in cardiovascular disease due to the increased mortality and prevalence of metabolic syndrome[1]. Various risk factors, including obesity, insulin resistance, dyslipidaemia, hypertension, and sedentary lifestyle, are associated with the development of metabolic syndrome[2]Obesity is one of the main risk factors for metabolic syndrome. Multiple research investigations have demonstrated that obesity is associated with insulin resistance, dyslipidemia, and hypertension, which are essential components of metabolic syndrome [3] Moreover, obesity is linked to chronic low-grade inflammatory response, which aids in the development of insulin resistance and other metabolic abnormalities[4]The metabolic syndrome is treated with a combination of lifestyle modifications and medication. The target of treatment is to reduce cardiovascular disease risk and enhance overall health *Effects of metformin monotherapy:*

Metformin is a commonly prescribed medication for type 2 diabetes treatment. Metformin is considered the primary pharmacological intervention for the management of type 2 diabetes. This mechanism functions by reducing glucose production in the liver. Recent research suggests that this strategy may be effective in the treatment of metabolic syndrome, a prevalent condition that affects roughly one-fourth of the world's adult population[5] Metformin is frequently combined with other pharmacological agents for the treatment of metabolic syndrome. According to scientific research, metformin monotherapy can produce beneficial results for metabolic syndrome. Metformin monotherapy is effective in improving glycemic control, weight loss, blood pressure, and lipid profile in individuals with metabolic syndrome, according to a 17-study metaanalysis and systematic review.[6] *Effects of SGLT-2 inhibitors:*

Inhibitors of sodium-glucose cotransporter-2 (SGLT-2) have emerged as a promising treatment option for metabolic syndrome. SGLT-2 inhibitors are a class of drugs that inhibit glucose reabsorption in the kidneys, resulting in increased glucose excretion in the urine. This mechanism of action reduces blood glucose levels and promotes weight loss. Inhibitors of SGLT-2 have also been shown to improve blood pressure, lipid profile, and cardiovascular outcomes. Dapagliflozin, empagliflozin, and canagliflozin are the most commonly utilised SGLT-2 inhibitors.

Effects of Metformin and SGLT-2 inhibitor combination therapy

Metformin alone or in combination with SGLT-2 inhibitors is an efficacious treatment for metabolic syndrome. It has been demonstrated that the combination of SGLT-2 inhibitors and metformin is more effective than metformin alone in increasing glycemic control, weight loss, blood pressure, and lipid profile. In a randomised, controlled trial involving 510 patients with type 2 diabetes and metabolic syndrome, the combination of dapagliflozin and metformin was found to be more efficacious than metformin monotherapy in terms of improving glycemic control, weight loss, and blood pressure. The combination of empagliflozin and metformin was more efficacious than metformin monotherapy in improving glycemic control, weight loss, blood pressure, and lipid profile in another randomised, controlled trial involving 1,233 patients with type 2 diabetes and metabolic syndrome [7]

METHODOLOGY

Patients Selected: The focus of this study was on adults older than 25 who have been diagnosed with metabolic syndrome. 48 patients with metabolic syndrome were selected as subjects for the study, and only those patients who gave their assent to participate in the research analysis were considered. All patients who participated in the trial were required to fill out an informed consent form in order to give their consent for the experiment. Patients who declined to participate in the research, who are pregnant, or who have been diagnosed with hepatitis are excluded from this study. All patients included in this study must have a GFR glomerular filtering rate of 45ml/min1.732 or greater.

Institutional Review Board / ethic committee Approval: TN/2018/RR-21/077; Vels Institute of Science Technology and Advanced Studies

Monitoring parameters and study method: The study evaluated various parameters, consisting of demographic characteristics comprising age, gender, and Body Mass Index (BMI). Laboratory investigations were conducted to assess the metabolic syndrome illness, with blood sugar parameters monitored for Diabetes Mellitus and blood pressure and thyroid stimulating hormone levels monitored for Hypertension. Dyslipidaemia lipid profile was also monitored, along with the inflammatory biomarker for CVD cardiovascular disease, hs(CRP) The selection of variables was based on the pathophysiology of the disease.

Statistical analysis: The statistical analysis involved reporting categorical variables as frequency percentages and continuous variables as means and standard deviations in the descriptive analysis. The present study employed bivariate analysis to investigate the correlation between categorical variables. Specifically, the Pearson's chi square test was utilised, and a two-tailed p value was deemed significant if it was less than 0.05, with a 95% confidence interval. The SPSS version 23 software was utilised for the purpose of conducting data analysis.

RESULTS

In this study forty eight patients completed this study, twenty four patients in metformin group and metformin and SGLT-2 inhibitor group respectively

TABLE :1 PATIENT DEMOGRAPHICS BASED ON AGE

AGE	**METFORMIN(n=24)**		**METFORMIN + SGLT-2 INHIBITORS (n=24)**	
	n	**%**	**n**	**%**
25-40	8	33.3%	9	37.5%
41-55	10	41.6%	11	45.8%
56-70	6	25%	4	16.6%

Baseline clinical characteristics of study participants are summarized in Table 1 and Table 2 most patients were middle aged (41-55 years) 43.75 % of the total patients participating in this study .Table 2 shows the gender baseline and the composition of this study had slightly more women participants (n=27) 56.25% of the total patients participating in this study were women and (n=21) 43.75% were men this indicates the prevalence of metabolic syndrome is higher in women when compared to male

TABLE :2 PATIENT DEMOGRAPHICS BASED ON GENDER

GENDER	**METFORMIN(n=24)**		**METFORMIN + SGLT-2 INHIBITORS (n=24)**	
	n	**%**	**n**	**%**
MALE	10	41.6%	11	45.8%
FEMALE	14	58.3%	13	54.2%
TOTAL	24	100%	24	100%

The total number of patients with metabolic syndrome participating in this study were split into two groups and each group consisting of 24 patients were administered with metformin and metformin with SGLT-2 inhibitors respectively 50% of total participants n=48

FIGURE:1 PATIENT DEMOGRAPHICS BASED ON AGE IN METFORMIN AND METFORMIN + SGLT-2 INHIBITORS

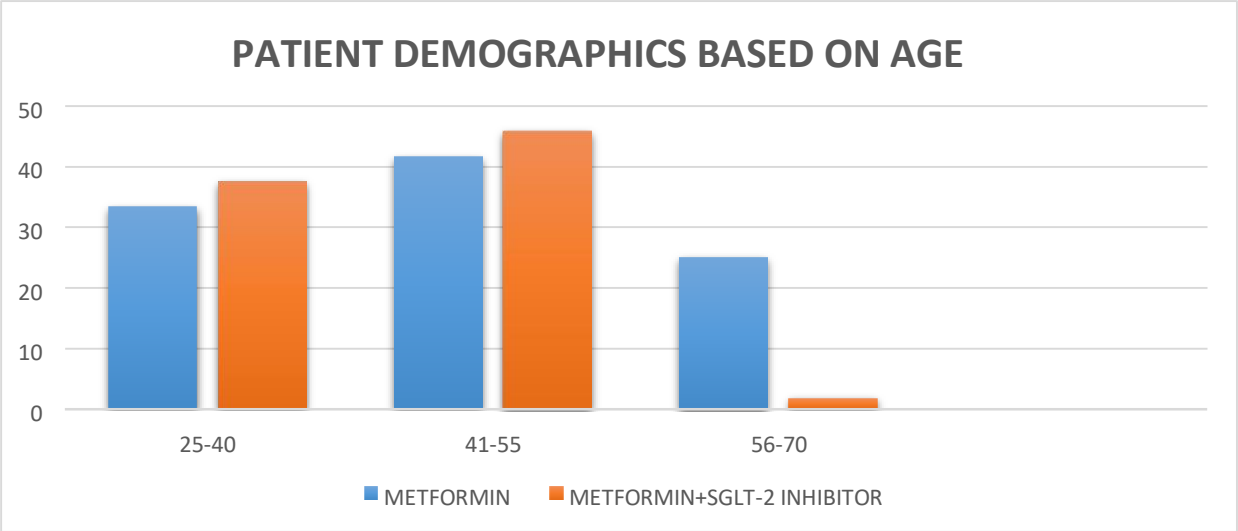
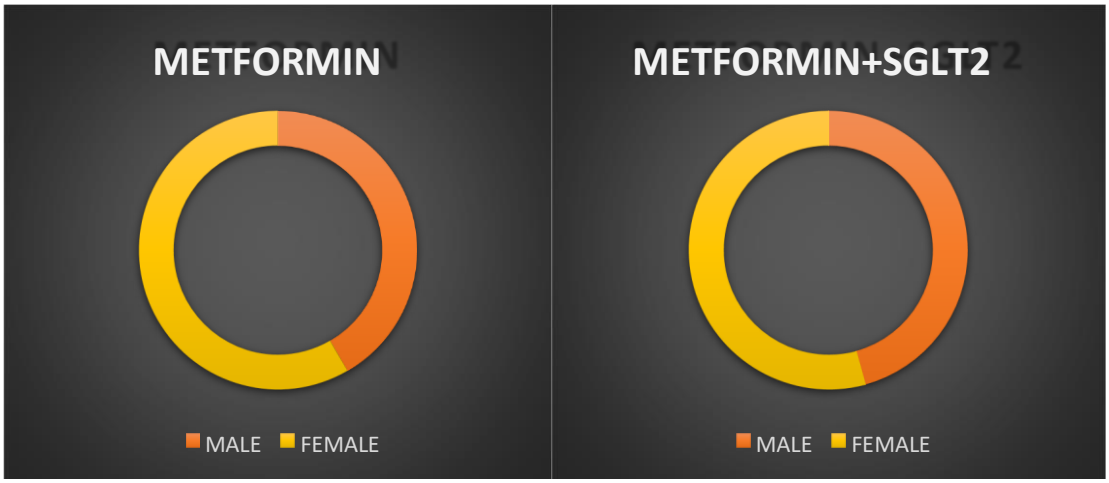


FIGURE:2 PATIENT DEMOGRAPHICS BASED ON GENDER



Obesity is one of the risk factors associated in metabolic illness over the study duration the height(centimeters) and weight (kilograms) were monitored to calculate BMI body mass index

TABLE :3 PATIENT DEMOGRAPHICS BASED ON BMI

PARAMETERS	**METFORMIN (n=24)**	**METFORMIN + SGLT-2 INHIBITORS (n=24)**	***P* VALUE**
	MEAN ± STD.ERROR	**MEAN ± STD.ERROR**	
HEIGHT	152.12 ± 1.28	150.62±1.177	0.608
WEIGHT	82.54 ± 0.92	81.62 ± 1.07	0.479
BMI	35.74 ± 0.58	36.08 ± 0..55	0.919

FIGURE:3 PATIENT DEMOGRAPHICS BASED ON BODY MASS INDEX (METFORMIN & METFORMIN + SGLT2)

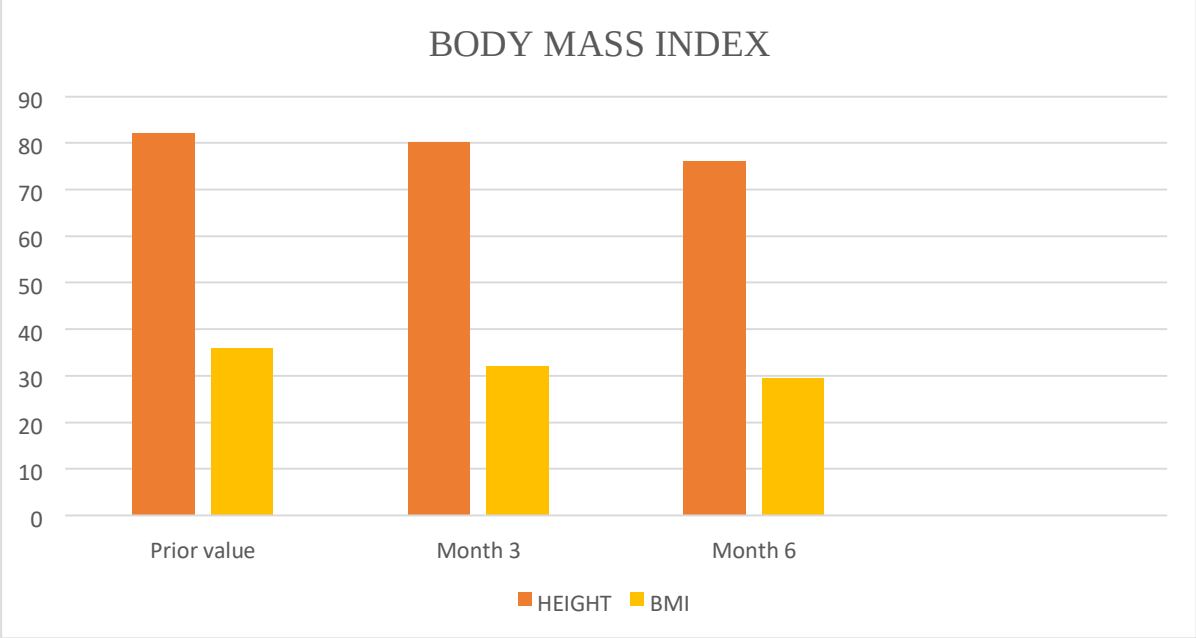


Table 4 and Table 5 shows the comparison difference of continuous variables mean and standard error of metformin monotherapy and metformin+SGLT-2 inhibitor in blood sugar levels of FBS, PPBS, HbA1C before and after therapy with 95% confidence interval Data are Mean ± Standard error unless otherwise stated, p value is chi square Pearson significance <0.05 *p* value therefore its statistically significant.

TABLE 4: COMPARISON OF DIFFERENCE OF BLOOD SUGAR PARAMETER IN METFORMIN AND METFORMIN +SGLT-2 INHIBITORS BEFORE THERAPY

PARAMETERS	**METFORMIN (n=24)**	**METFORMIN + SGLT-2 INHIBITORS (n=24)**	***P* VALUE**
	MEAN ± STD.ERROR	**MEAN ± STD.ERROR**	
FBS	254.45 ± 15.093	237.79 ± 5.73	0.061
PPBS	294.66 ± 10.17	277.00 ± 11.44	0.056
HbA1C	7.95 ± 0.15	6.712 ± 0.37	0.00

TABLE 5:

COMPARISON OF DIFFERENCE OF BLOOD SUGAR PARAMETER IN METFORMIN AND METFORMIN +SGLT-2 INHIBITORS AFTER THERAPY

PARAMETER	**METFORMIN (n=24)**	**METFORMIN + SGLT-2 INHIBITORS (n=24)**	***P* VALUE**
	MEAN ± STD.ERROR	**MEAN ± STD.ERROR**	
FBS	293.70 ± 10.877	290.91 ± 9.79	0.662
PPBS	363.25 ± 14.52	338.166 ± 13.57	0.778
HbA1C	9.00 ±0.11	8.05 ± 0.210	0.005

FIGURE:4 FBS (FASTING BLOOD SUGAR)(METFORMIN & METFORMIN +SGLT2)

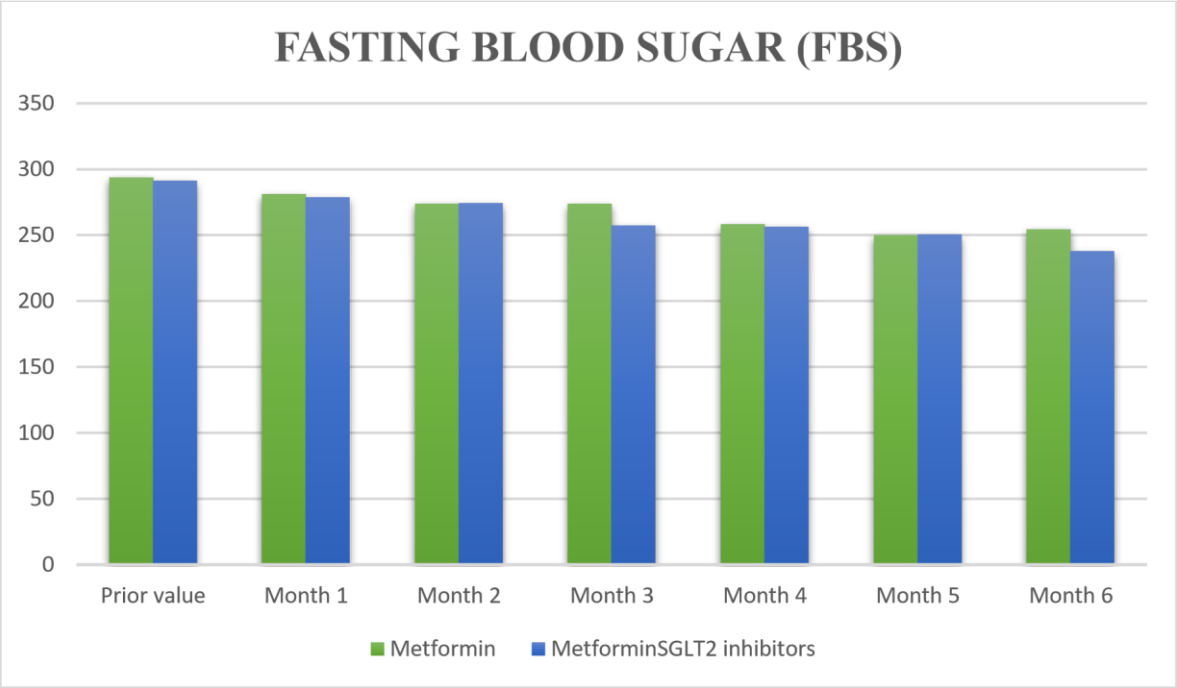


FIGURE:5 PPBS (POST PRANDIAL BLOOD SUGAR)(METFORMIN & METFORMIN +SGLT2)

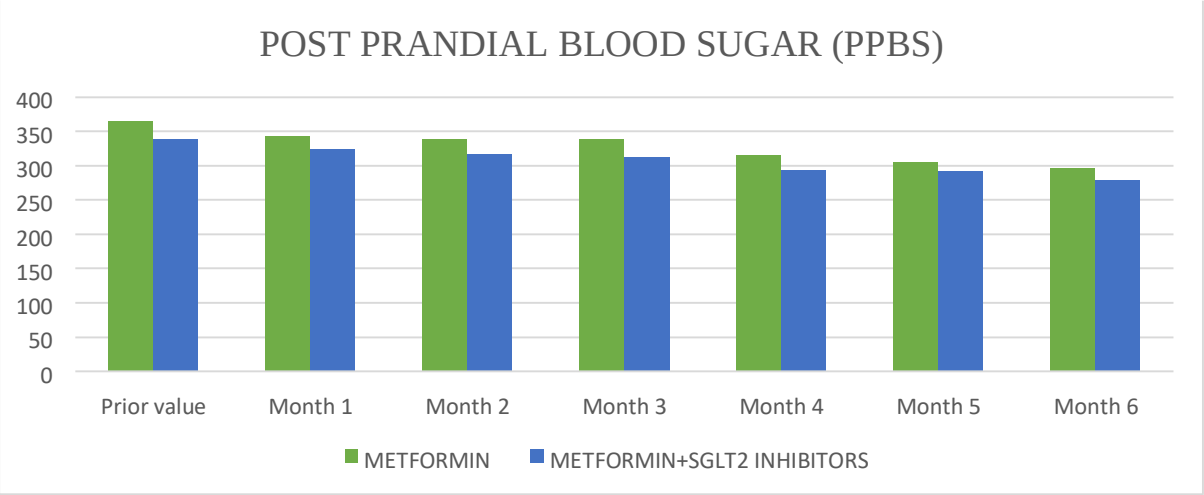


FIGURE: 6 HbA1C (METFORMIN & METFORMIN +SGLT2)

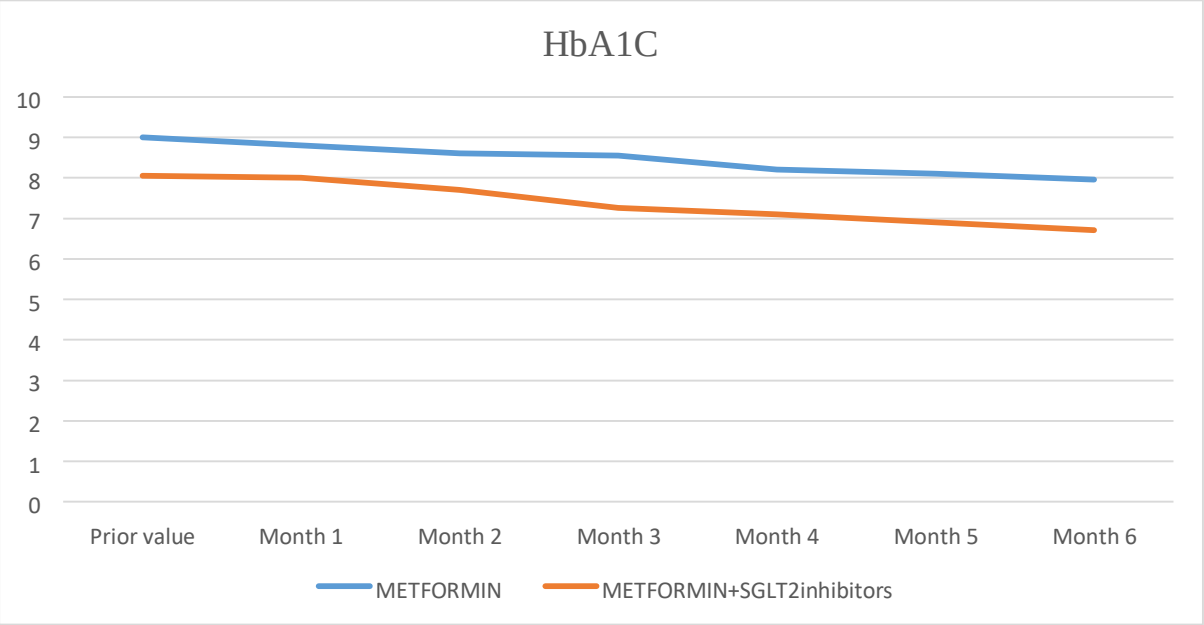


Table 6 and Table 7 shows the comparison difference of continuous variables mean and standard error of metformin monotherapy and metformin+SGLT-2 inhibitor in blood pressure SYSTOLIC PRESSURE (mm/hg) DIASTOLIC PRESSURE (mm/hg) before and after therapy with 95% confidence interval Data are Mean ± Standard error unless otherwise stated, p value is chi square Pearson significance <0.05 p value therefore its statistically significant.

TABLE 6: COMPARISON OF DIFFERENCE OF BLOOD PRESSURE IN METFORMIN AND METFORMIN +SGLT-2 INHIBITORS BEFORE THERAPY

PARAMETERS	**METFORMIN (n=24)**	**METFORMIN + SGLT-2 INHIBITORS (n=24)**	***P* VALUE**
	MEAN ± STD.ERROR	**MEAN ± STD.ERROR**	
SYSTOLE BP (mm/hg)	132.58 ± 1.49	131.29 ± 1.484	0.968
DIASTOLE BP (mm/hg)	87.91 ± 1.079	87.08 ± 1.079	0.987
TSH	1.55 ± 0.130	3.94± 0.149	0.282

TABLE 7: COMPARISON OF DIFFERENCE OF BLOOD PRESSURE PARAMETER IN METFORMIN

AND METFORMIN +SGLT-2 INHIBITORS AFTER THERAPY

PARAMETERS	**METFORMIN (n=24)**	**METFORMIN + SGLT-2 INHIBITORS (n=24)**	***P* VALUE**
	MEAN ± STD.ERROR	**MEAN ± STD.ERROR**	
SYSTOLE BP (mm/hg)	123.91 ± 1.497	117.95 ± 1.308	0.733
DIASTOLE BP (mm/hg)	83.66 ± 1.048	77.08 ± 1.079	0.757
TSH	3.33 ± 0.148	3.24 ± 0.149	0.011

FIGURE: 7 SYSTOLIC PRESSURE (METFORMIN & METFORMIN +SGLT2)

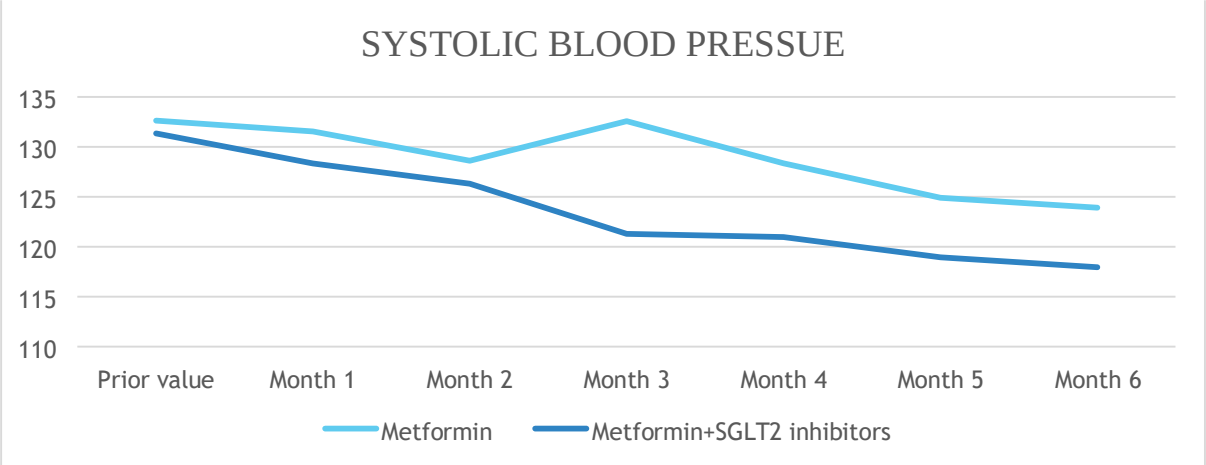


FIGURE: 8 DIASTOLIC PRESSURE (METFORMIN & METFORMIN +SGLT2)

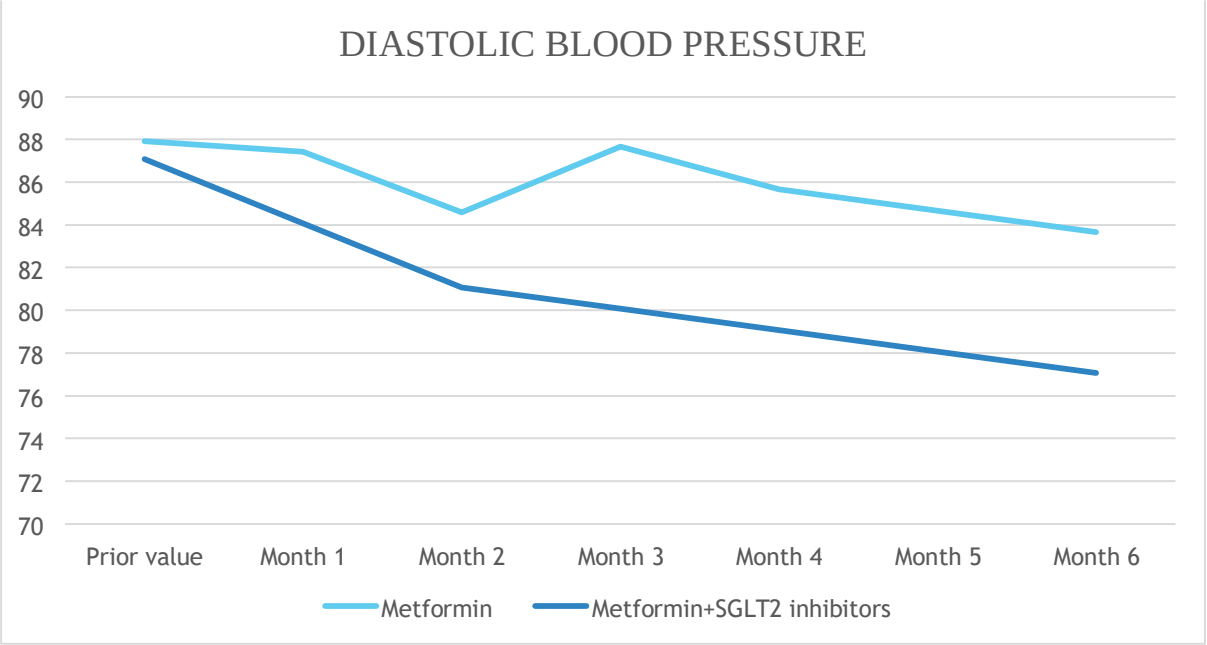


FIGURE: 9 THYROID STIMULATING HORMONE (METFORMIN & METFORMIN +SGLT2)

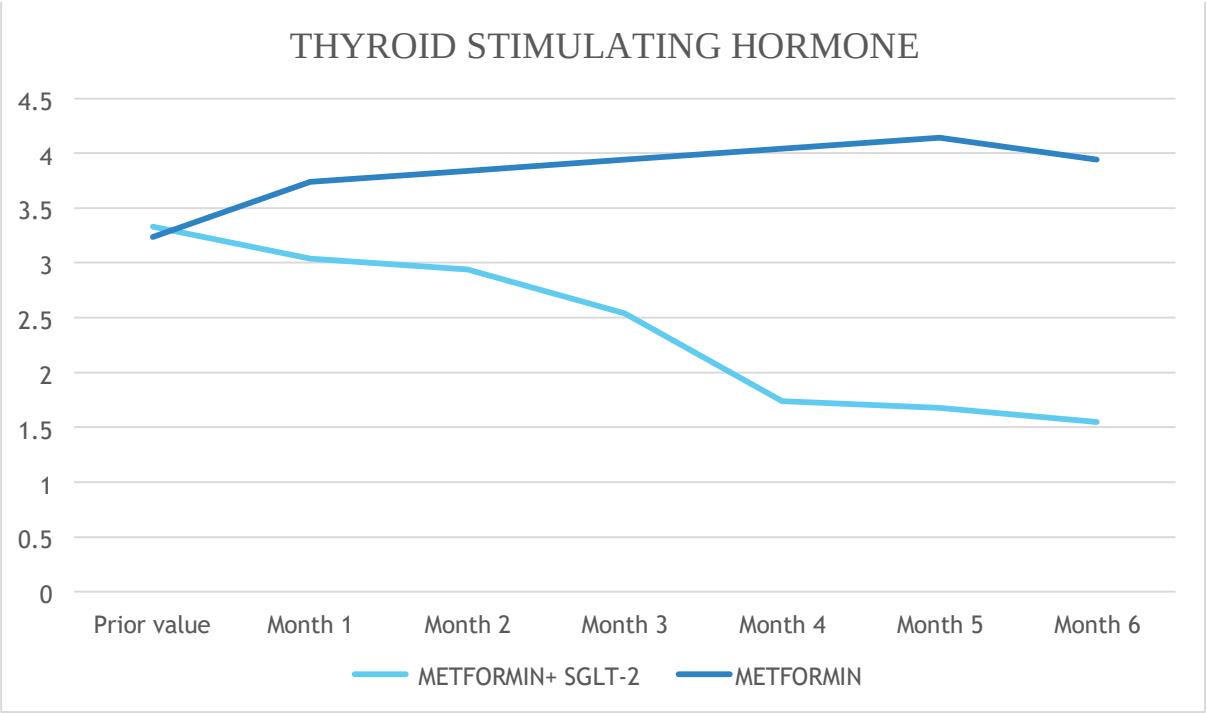


Table 8 and Table 9 shows the comparison difference of continuous variables mean and standard error of metformin monotherapy and metformin+SGLT-2 inhibitor in lipid profile HDL high density lipo protein, LDL low density lipoprotein, TG triglycerides before and after therapy with 95% confidence interval Data are Mean ± Standard error unless otherwise stated, p value is chi square Pearson significance <0.05 p value therefore its statistically significant.

TABLE 8: COMPARISON OF DIFFERENCE OF LIPID PROFILE PARAMETER IN METFORMIN AND

METFORMIN + SGLT-2 INHIBITORS BEFORE THERAPY

PARAMETERS	**METFORMIN (n=24)**	**METFORMIN + SGLT-2 INHIBITORS (n=24)**	***P* VALUE**
	MEAN ± STD.ERROR	**MEAN ± STD.ERROR**	
HDL	65.33 ± 1.693	76.66 ± 3.09	0.002
LDL	151.45 ± 2.502	176.45 ± 3.345	0.625
TG	224.91 ±5.08	232.20 ± 5.55	0.490

TABLE 9: COMPARISON OF DIFFERENCE OF LIPID PROFILE PARAMETER IN METFORMIN AND METFORMIN + SGLT-2 INHIBITORS AFTER THERAPY

PARAMETERS	**METFORMIN (n=24)**	**METFORMIN + SGLT-2 INHIBITORS (n=24)**	***P* VALUE**
	MEAN ± STD.ERROR	**MEAN ± STD.ERROR**	
HDL	78.20 ± 2.345	89.79 ± 2.026	0.230
LDL	158.95 ± 2.469	146.75 ± 1.94	0.511
TG	236.91 ± 6.134	232.33 ± 2.301	0.001

FIGURE: 10 HIGH DENSITY LIPOPROTEIN (METFORMIN & METFORMIN +SGLT2)

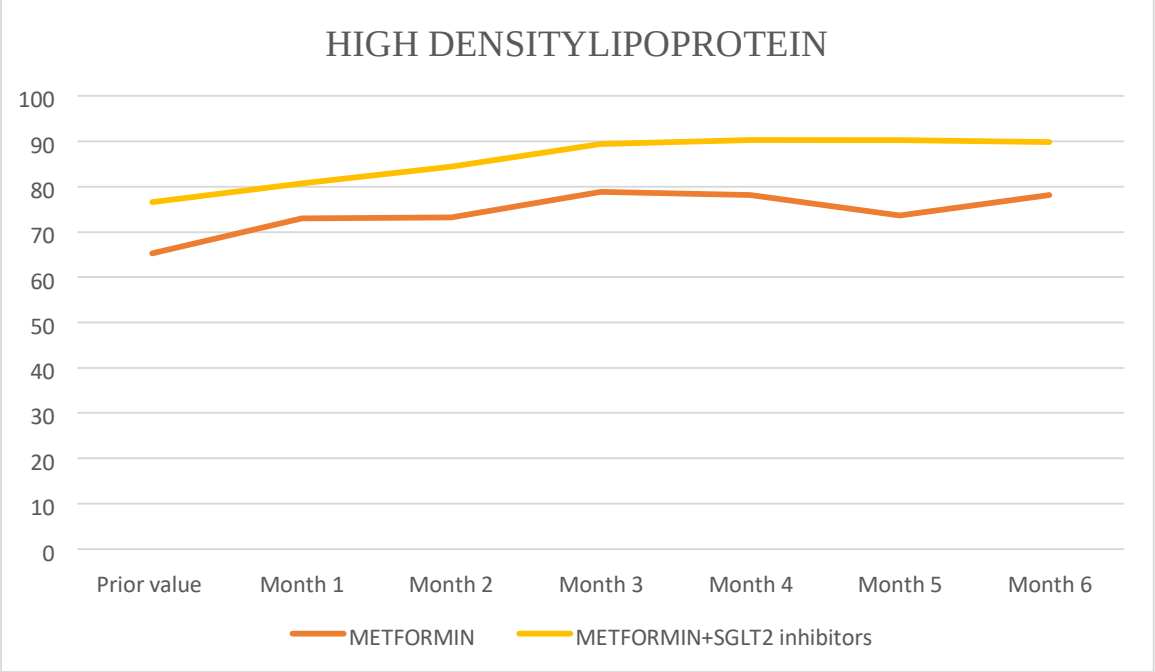


FIGURE: 11 LOW DENSITY LIPOPROTEIN (METFORMIN & METFORMIN +SGLT2)

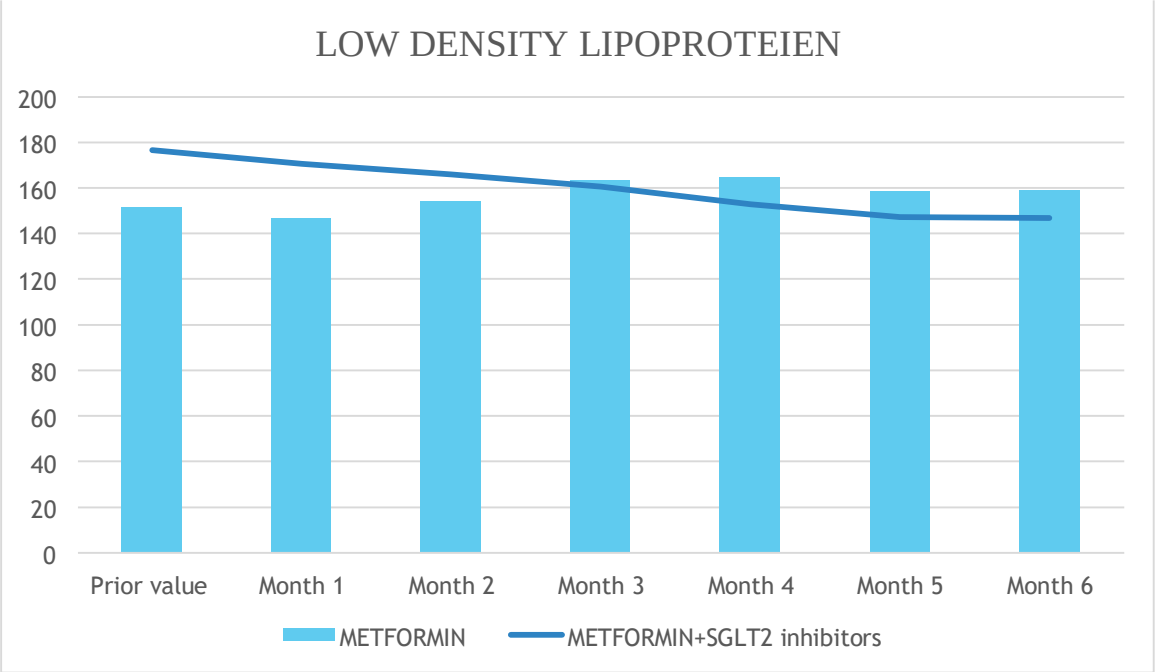


FIGURE: 12 TRIGLYCERIDES (METFORMIN & METFORMIN +SGLT2)

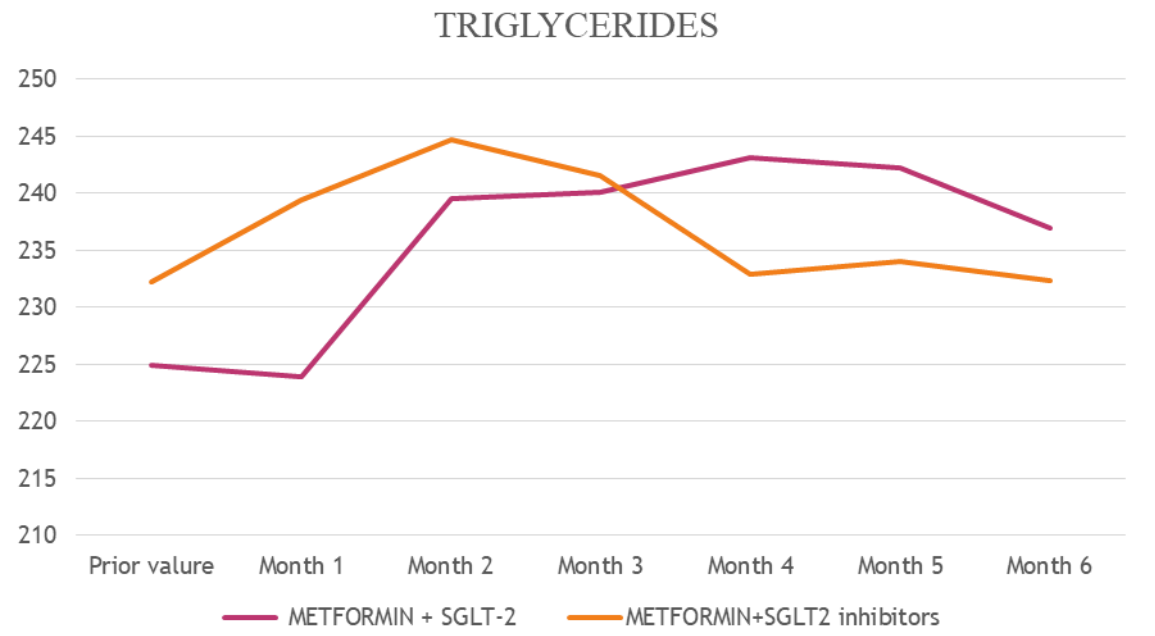


Table 10 and Table 11 shows the comparison difference of continuous variables mean and standard error of metformin monotherapy and metformin+SGLT-2 inhibitor in inflammatory markers for CVD cardiovascular disease hs(CRP) high sensitivity C-reactive protein before and after therapy with 95% confidence interval Data are Mean ± Standard error unless otherwise stated, p value is chi square Pearson significance <0.05 p value therefore its statistically significant.

TABLE 10: COMPARISON OF DIFFERENCE OF INFLAMMATORY INDICATOR PARAMETER IN

METFORMIN AND METFORMIN + SGLT-2 INHIBITORS BEFORE THERAPY

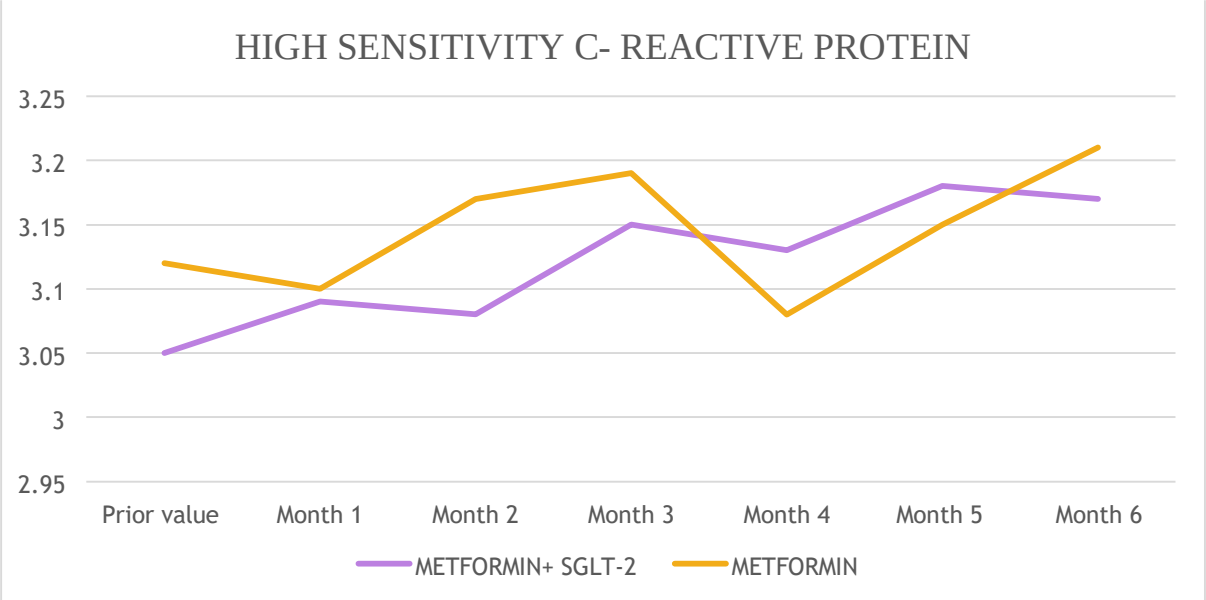
PARAMETERS	**METFORMIN (n=24)**	**METFORMIN + SGLT-2 INHIBITORS (n=24)**	***P* VALUE**
	MEAN ± STD.ERROR	**MEAN ± STD.ERROR**	
h(CRP)	3.21 ± .044	3.17 ± 0.030	0.690

TABLE 11: COMPARISON OF DIFFERENCE OF INFLAMMATORY INDICATOR PARAMETER IN

METFORMIN AND METFORMIN + SGLT-2 INHIBITORS AFTER THERAPY

PARAMETERS	**METFORMIN (n=24)**	**METFORMIN + SGLT-2 INHIBITORS (n=24)**	***P* VALUE**
	MEAN ± STD.ERROR	**MEAN ± STD.ERROR**	
h(CRP)	3.05 ± 0.020	3.12 ± 0.0414	0.396

FIGURE: 13 HIGH SENSITIVITY C-REACTIVE PROTEIN (METFORMIN & METFORMIN +SGLT2)



DISCUSSION

This study was a prospective investigation carried out at a tertiary care centre with a government emphasis, taking inspiration from diverse international studies conducted across the globe. The present investigation elucidates the impact of SGLT_2 inhibitors in conjunction with metformin versus metformin monotherapy on the management of metabolic syndrome.

The aim of this study is to assess the clinical effectiveness of the addition of SGLT2 inhibitors to metformin therapy in patients with metabolic syndrome, in comparison to metformin monotherapy. The ultimate goal is to enhance patient treatment outcomes and enhance their overall quality of life. Furthermore, the research endeavours to examine the function of SGLT-2 inhibitors in the management of type-2 diabetes patients who are susceptible to cardiovascular complications. It is imperative to establish a therapeutic protocol or regimen that considers the accessibility of pharmaceuticals and diagnostic characteristics, as well as the financial circumstances of the patient. This will offer a logical basis for the utilisation of SGLT-2 inhibitors in conjunction with a metformin treatment plan. The justification for the amalgamation of SGLT-2 inhibitors and metformin as the primary intervention for diabetic therapy has been expounded upon in the directives of the American Association of Clinical Endocrinologists and the Canadian Diabetes Association [8]

The study participants were within the age range of 25 to 70 years, as indicated by the notation >25 and <70[9]. They were divided into two groups, with each group receiving either metformin monotherapy or a combination of metformin and SGLT-2 inhibitors. The study monitored various therapeutic variables, including the inflammatory biomarker CRP and thyroid stimulating hormone levels, in addition to BMI, FBS, PPBS, TG, systolic and diastolic blood pressure, and lipid profile.

Our study, akin to the investigation conducted by D. S. Prasad et al., revealed a greater prevalence of females, accounting for 56.25% of the sample, in contrast to males[10]. Furthermore, our investigation has demonstrated that the administration of SGLT2 inhibitors is linked to favourable cardio metabolic outcomes, including reductions in body weight and blood pressure, as well as enhancements in lipid profiles. These results exhibit resemblance to the research conducted by Lakshini Y. Herat et al. in their study[11]. According to research findings, hsCRP is considered the most effective biomarker in individuals diagnosed with metabolic syndrome. This conclusion is supported by a study published in the journal of Clinical Chemistry and Laboratory Medicine. Given that inflammation is a marker for metabolic syndrome. In a recent study, Jialal et al. have suggested that the ratios of neutrophils and monocytes to high-density lipoprotein-cholesterol may serve as more effective predictors of metabolic syndrome compared to hs CRP alone[12]Therefore, our study evaluated two interventions targeting inflammatory markers and demonstrated equivalent improvements in patients treated with metformin and SGLT-2 inhibitors.

Our research is among the limited number of studies that have assessed the impact of SGLT-2 inhibitors in conjunction with metformin and metformin alone on metabolic parameters. The results of the study indicate that a combined therapy of SGLT-2 inhibitors and metformin could be a more advantageous initial treatment alternative for patients with metabolic syndrome, as it exhibited superior benefits and advantages in comparison to monotherapy.

Similar to prior investigations, our research exhibits certain constraints. The study was limited by a relatively small sample size and a narrow focus on administering definitive treatment exclusively to a subset of patients with metabolic syndrome who are particularly relevant to treatment

management in this condition. The study was deficient in a standardized treatment regimen for SGLT-2 inhibitors, which hindered the evaluation of individualized drugs under SGLT-2 inhibitors like dapagliflozin, canagliflozin, and empagliflozin medication responses. This was due to the fact that medication prescriptions were based on drug availability and financial circumstances. In order to investigate the impact of various variables on the cardiovascular benefits and safety profile of SGLT-2 as a monotherapy for metabolic syndrome, it is imperative to conduct research on a sizable population with more targeted therapeutic characteristics.

CONCLUSION:

In treatment with metformin monotherapy and SGLT-2 inhibitors with metformin combination therapy the add on therapy generally showed more efficacy in improvement of HbA1C levels, blood pressure, and lipid profile along with BMI and h(CRP) levels collectively The present study is anticipated to contribute to physicians' and clinical chemists' understanding of metabolic syndrome and its treatment. Specifically, it seeks to cast light on the pertinent factors that must be considered in the management of metabolic syndrome. In addition, it is anticipated that the study will increase awareness of metabolic syndrome and promote preventive measures against it through the development of effective prevention and management strategies considering the benefits of SGLT-2 inhibitors a novel drug therapy in management of metabolic syndrome

The authors have declared that no competing interests exist and no conflict of interests in publishing this paper.

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