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THE IMPACT OF THERAPEUTIC AND LIFESTYLE MODIFICATION OUTCOMES ON METABOLIC RISK MARKERS IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

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ABSTRACT:

Metabolic syndrome is a condition characterized by a group of risk factors that increase the risk of cardiovascular disease and type 2 diabetes. Metabolic syndrome is a constellation of interrelated risk factors with mostly promote atherosclerotic cardiovascular disease.

Methods: Patients were assigned randomly in eight groups based on the plan of study. Various health indicators compared include weight, BMI, systolic and diastolic blood pressure, fasting blood sugar, glycated hemoglobin, triglycerides and HDL.

Results: We found the risk of hypertension was 23% lower in females than males with metabolic syndrome. No other parameter had correlation with gender. When comparing among the groups for the parameters; group 5 had higher mean values of weight and BMI than group 1, the two groups had significant impact on weight BMI, blood pressure, glycemic parameters. Group 1 had lower mean values of triglycerides and HDL than group 5. Group 7 was more effective than group 3 in reducing weight and BMI, group 7 was associated with lower blood pressure, glycemic parameters and higher HDL than group 3.

Conclusion: Overall our study concluded that lifestyle modification is necessary in improving all parameter compared with other groups, with augmented effect upon pharmacological intervention. The effect was significant in groups without metabolic syndrome.

Keywords: *Metabolic syndrome, Lorcaserin, Obesity, Diabetes Mellitus, lifestyle modification*

INTRODUCTION

Metabolic syndrome is a group of disease that occur together, increasing the risk of cardiac disease, stroke, and diabetes. The conditions that make up metabolic syndrome include Abdominal obesity: having a waist circumference greater than 40 inches (men) or 35 inches (women), High blood pressure of 130/85 mm Hg or higher, High blood sugar of 100 mg/dL (fasting) or higher, High triglycerides of 150 mg/dL or higher, Low HDL cholesterol of less than 40 mg/dL (men) or less than 50 mg/dL (women)(1,2). The prevalence of metabolic syndrome has is on the rise globally, it is estimated that it affects about 25% adults worldwide [(3,4)].The condition is more prevalent in developed countries, where sedentary lifestyles and poor dietary choices are common [(4,5)]. Metabolic syndrome is becoming increasingly common due to rising obesity rates, lack of physical activity, and poor dietary choices. It is important to manage the individual conditions that make up metabolic syndrome through lifestyle changes, like healthy eating, regular exercise, and medication as needed, in order to reduce the risk of

developing cardiac, neurological and metabolic diseases [4,6].

There is increasing evidence to support the link between metabolic syndrome and cardiovascular disease. Various studies have shown that people with metabolic syndrome are twice as likely to develop cardiovascular disease in comparison to those without [4]. The presence of metabolic syndrome is also associated with an increased risk of developing type 2 diabetes, which further increases the risk of cardiovascular disease [4]. The exact cause of metabolic syndrome is not fully understood, it is thought to stem from a combination of genetic and environmental factors [5,6].Lifestyle factors such as physical inactivity, diet high in saturated fat, sugars, and smoking have all been implicated in the development of metabolic syndrome. The treatment of metabolic syndrome involves a combination of lifestyle modifications, such as weight loss, regular exercise, and dietary changes, as well as pharmacological interventions. Lifestyle modifications have demonstrated the effectiveness in reducing the risk for cardiovascular disease and improving overall health outcomes[6].

METHODOLOGY

Our study is a randomized, prospective clinical intervention study aimed at investigating the effects of lorcaserin on metabolic syndrome. Group 1 to 4 had metabolic syndrome. Group 5 to 8 did not have metabolic syndrome. The study population consists of eligible patients who are diabetic and obese or overweight, having a BMI range of 27 to 45 kg/m2 with at least one obesity-related co-morbid condition. The patients are categorized into eight groups, based solely on the treatments prescribed to each group and the primary and secondary outcomes are documented and analyzed. The eligible patients were randomly assigned in a 1:1 ratio to receive one of eight treatments: Group 1, 5 received lorcaserin with SGLT2 inhibitors and lifestyle modifications; Group 2, 6 received SGLT2 inhibitors and lifestyle modifications, but no lorcaserin; Group 3,7 received lorcaserin with SGLT2 inhibitors, but no lifestyle modifications; and Group 4, 8 received SGLT2 inhibitors only, and no lifestyle modifications or lorcaserin. All patients randomized for the lifestyle modification program were encouraged to do active physical exercise, limit calorie intake based on a diet chart provided by physicians or dietitian, and increase consumption of fruits, vegetables, whole grains, and nuts during each visit. Study was approved by the institutional ethics board: EC/AP/578/2/2018.

Inclusion criteria

The study population had to have at least two of the following criteria to be included: (a) systolic blood pressure (SBP) ≥130 mmHg, diastolic blood pressure (DBP) ≥85 mmHg, (b) serum triglycerides (TGL): ≥150 mg/dL, (c) high-density lipoprotein (HDL) cholesterol: < 40 mg/dL for males and < 50 mg/dL for females, (d) fasting glucose (FG): ≥100 mg/dL.

Exclusion criteria

The exclusion criteria were absolute contraindication for physical activity due to musculoskeletal, neurological, vascular, lung or cardiac problems, pregnancy, gestational diabetes and lactating mothers, diagnosis of severe psychiatric illness, severe cognitive impairment, and inability to participate in the program owing to personal conflicts.

Assessment plan

Anthropometric parameters such as weight, height and BMI, as well as glycaemic parameters such as fasting blood sugar and HbA1c, and cardiometabolic parameters such as systolic and diastolic blood pressure, triglycerides, and HDL were documented at baseline (visit 1) for all patients included in the study. Follow-up monitoring was done at week 12 (Visit 2) and week 24 (Visit 3). The aim of the study was to compare the treatment regimen of patients with and without metabolic syndrome and to analyze the result using different parameters tested within the groups. The primary patient safety outcome was to monitor primary cardiovascular events such as cardiovascular death, myocardial infarction and stroke, while quality of life changes associated with the outcomes were kept as secondary measures for analysis. The study used statistical analysis to

evaluate the data collected. Comparison data was performed using unpaired t-test or Fischer exact test. The p-value for this test is significant at 0.05.

RESULTS

Study included 350 patients with metabolic syndrome (Group 1 to 4) and 384 without metabolic syndrome (Group 5 to 8). We aimed to analyze gender association with co-morbidities & found no significant changes in any of the parameters among the groups except for BMI in Group 1.

Table 1: Comparing the mean values and p value various parameters among the groups 1 & 5, 2 & 7 withand without metabolic syndrome

Parameters	Group 1 vs Group 5			Group 3 vs Group 7		
	G1	G5	p value	G3	G7	p value
Weight	73.11	79.02	***	74.03	78.36	***
BMI	28.27	27.6	***	28.84	27.3	***
Systolic BP	134.47	123.02	***	132.1	120	***
Diastolic BP	80	87.79	***	78.23	86	***
FBS	202.09	151.05	***	210.06	152.77	***
HbA1c	8.15	7.04	***	8.99	7	***
TGL	146.45	152.79	***	153.74	149.01	***
HDL	49.83	53.06	***	49.58	39.93	***

The significance level of the differences between the two groups is indicated by the p value column in the table. The three asterisks (***) next to the p values indicate that the differences between the two groups are statistically significant. ns - not significant. Group 1, 5 received pharmacological intervention with SGLT2 inhibitors and lifestyle modifications; Group 3,7 received pharmacological intervention with SGLT2 inhibitors, but no lifestyle modifications.

Table 2: Comparing the mean values and p value various parameters among the groups 2 & 6 , 4 & 8 withand without metabolic syndrome

Parameters	Group 2 Vs Group 6			Group 4 Vs Group 8		
	G2	G6	p-value	G4	G8	p-value
Weight	73.32	80.01	***	75.17	73.78	ns
BMI	28.08	27.9	ns	27.46	28.63	***
Systolic BP	132.82	122.25	***	127.81	127.24	ns
Diastolic BP	80.7	87.46	***	81.09	80	ns
FBS	204.82	157.55	***	186.06	193.79	ns
HbA1c	8.69	7.07	***	8.2	8.13	ns
TGL	159.38	151.75	***	151.56	163.46	***
HDL	38.68	51.41	***	43.47	37.93	***

The significance level of the differences between the two groups is indicated by the p value column

in the table. The three asterisks (***) next to the p values indicate that the differences between the two groups are statistically significant. ns - not significant. Group 2, 6 received SGLT2 inhibitors and lifestyle modifications, but not pharmacological intervention and Group 4, 8 received SGLT2 inhibitors only, and no lifestyle modifications or pharmacological intervention.

Patients with metabolic syndrome

In the metabolic syndrome group 109 of 350 males had hypertension, and 77 of the female patients (n=123) had hypertension. Fisher's exact test was used to determine whether there was a statistically significant relationship between the parameters and gender. The test resulted in a P-value of 0.0100, (RR: 0.767, 95% CI: 0.6344-0.9342) indicating that there is a statistically significant association between hypertension and gender. The risk of high blood pressure is 23% lower in women than in men. The odds ratio (OR) was 0.5518 with a 95% CI of 0.3489 to 0.8539, indicating that women are approximately 55% more likely to develop hypertension than men.

The association of dyslipidemia (presence or absence) and gender (male or female) was analyzed. The P value for the test is 0.3112. The effect sizes, represented by relative risk and odds ratio are close to 1, further indicating that there is no significant association between the two variables and they indicate that dyslipidemia is more prevalent in males than in females, but the difference is not statistically significant. For dyslipidemia the relative risk is 0.8981, which indicates that the risk of having dyslipidemia is slightly lower for males than for females. The odds ratio is 0.7819, which also suggests a slightly lower odds of having dyslipidemia among males compared to females. For cardiovascular diseases, the relative risk is 1.126 (95% CI: 0.9412 - 1.373) indicating that the risk of having cardiovascular diseases is slightly higher for females than for males. The odds ratio is 1.335 (95% CI: 0.8586 - 2.065), slightly higher odds of having cardiovascular diseases among women compared to men. Obstructive sleep apnea was irrelevant, p-value 0.7372 (RR: 0.9547, 95% CI: 0.7723-1.195; OR: 0.9113, 95% CI: 0.5936-1.396) and for EDS, P value 0.4337 with a RR of 0.9113 (95% CI:0.7415 - 1.133) and OR 0.8264 (95% CI:0.5366 - 1.298) indicating that OSA & EDS are independent of gender.

Patients without metabolic syndrome

In the population without metabolic syndrome (n=384) when the association between various comorbidities and gender were calculated, EDS was significant with a p-value of 0.003 (OR 0.5056, 95% CI: 0.3261-0.7814 and RR 0.6716, 95% CI: 0.5268-0.8657). None of the other co-morbidities had association with gender. No association for hypertension, p value 0.8249 (OR: 1.056, 95% CI: 0.6760-1.612 and RR 1.028, 95% CI: 0.8294-1.298). Dyslipidemia in diabetic population was also independent of gender p = 0.5786, OR 1.154 (95% CI: 0.7392-1.769) RR 1.078 (95% CI: 0.8625-1.374). Cardiovascular disease was also not associated with gender, p value 0.3698, OR 1.230 (95% CI: 0.7784-1.938), RR 1.131 (95% CI: 0.8721-1.497).

Group 1 Vs Group 5

When comparing group 1 and group 5 who received same therapy with variation in the fact that group 1 had metabolic syndrome and group 5 did-not. The t-test results show that there is a significant difference in weight and BMI between group 1 and 5. Group 5 had a higher mean value for body weight and lower mean BMI than Group 1. The t-value for weight was -6.49, and for the t-value for BMI was 1.83. The p-value for weight was < 0.00001, and p-value for BMI was 0.034904, indicating the difference between the sample means is statistically significant. These results suggest that group 5 (without metS) may be effective in reducing body weight, but less effective in reducing BMI. BMI values were lower in group 1 (with metS) suggesting better long-term treatment outcome compared to group 5.

For the Systolic BP variable, the t-value is 7.64192 and the p-value of <.00001, indicating a significant difference between the two groups. For

the diastolic BP variable, the t-value is -7.05124 and the p-value of <.00001, which also indicates that there is significant difference between the two groups. These results suggest that the two treatments have a large impact on the two variables. For FBS, there was a significant difference between the means of the two groups with a t-value of 12.65698 and a p-value of less than 0.00001. This suggests that the difference in means was probably not random and the two groups did indeed have different effects on FBS levels. HbA1c was also significantly different between the means of the two groups, with a t-value of 7.07205 and a p-value of less than 0.00001. The two groups had differential effects on HbA1C levels making it unlikely that difference were due to chance.

Group 5 had a significantly higher mean triglyceride (M2 = 152.79) than group 1 (M1 = 146.45), with a t-value of -10.79975 and a p-value of < .00001. The same pattern was observed for HDL cholesterol, with group 5 having a significantly higher mean (M2=53.06) than group 1 (M1=49.83), with a t-value of -9.21049 and a p-value of < .00001. Both the groups had significant changes in lipemia profile, which may be because of the SGLT2 inhibitor used which has effect on effect on cholesterol.

Group 3 Vs Group 7

The result for weight & BMI showed a significant difference between Group 3 & Group 7 at a p value of < 0.05 . The t-value for weight was -2.87 and p-value was 0.002371, while the t-value for BMI was 2.70 and p value was 0.003945 . Suggesting that Group 7 may be more effective that Group 3 for both Weight & BMI. For the Weight variable, the t-value is negative (-2.87), indicating that Group 3 has a significantly lower weight than group 7 (p value: 0.002). For the BMI variable, the t-value is positive (2.70), indicating that Group 3 has a significantly higher BMI than Group 7 (p-value is 0.004). As these groups did not receive lorcaserin the variation in BMI or weight was not static. For Systolic BP difference between Group 3 & 7 was significant at p < 0.05, with t-value of 4.5194 & p-value of 0.00001. Group 7 was associated with lower BP compared with Group 3 for both Systolic & Diastolic BP. For FBS, the t-value is 8.66 & p-value < 0.00001, for HbA1C the value is 7.99 & p-value < 0.00001 is significant indicating the difference between the two treatment groups. For Triglycerides, the t-value is 2.04 & p-value 0.021, indicating that the difference between the two treatment groups is significant at p < 0.05. For HDL variation, t-value of 14.24, Group 3 had mean of 49.58 & Group 7 had mean 39.93. Overall Group 3 has a significantly higher mean than Group 7. For the Sys BP variable, the t-value is positive (4.52), indicating that group 3 has a significantly higher Sys BP than group 7 (p-value is less than 0.0001), whereas Diastolic BP variable, the t-value is negative (-3.23), indicating that group 7 has a significantly higher Diastolic BP than group 3 (p-value is 0.001).

Group 2 Vs Group 6

Comparing the effects of the two groups (G2 and G6) on body weight, BMI, systolic blood pressure, and diastolic blood pressure. The analysis revealed a significant weight difference (p<0.05) between G2 and G6, with a mean weight of 73.32 for G2 and 80.01 for G6. However, there was no significant difference between the two groups in terms of BMI (p > 0.05), with a mean BMI of 28.08 for G2 and 27.92 for G6. Regarding blood pressure, there was a significant difference in systolic pressure (p < 0.05), with a mean systolic pressure of 132.82 for G2 and a mean systolic pressure of 122.25 for G6, but no difference in diastolic pressure (p > 0.05). .05). where G2 is the mean systolic blood pressure of 132.82. mean diastolic blood pressure of 80.7, and that of G6 is 87.46. The t value for HbA1C was 7.99 and the result was significant with p < 0.00001. For triglycerides, the t-value was 13.01 and the result was significant with p<0.00001. For HDL, the t-value was -30.32 and the result was significant with p<0.00001. Overall, the results suggest that group 6 is associated with greater improvement in all three health markers compared to group 2. Specifically, group 6 was associated with lower HbA1C and triglyceride levels and higher HDL levels.

Group 4 Vs Group 8

There is a significant difference in BMI between Group 4 and Group 8, but not in weight. Weight has a t-value 1.45418, and a p-value of .074083, not significant at $p < .05$. BMI has a t-value of -3.49277, and a p-value of 0.000321, significant at $p < .05$ this may be the effect of SGLT2 inhibitor. For the Systolic BP difference values, the t-value was 0.21425 with a p-value of 0.415335. For the Diastolic BP difference values, the t-value was 0.75645 with a p-value of 0.225334. The values of blood pressure didnot show significant change between the groups during follow up period. FBS difference was calculated, the t-value was -0.9171 with a p-value of 0.180. For the HbA1C difference values, the t-value was -0.026 with a p-value of .979906. In all cases, the p-value were above the threshold of .05, indicating no significant difference between the two groups for each respective outcome measure. For triglycerides, the t-value is -24.39352 with a p-value is < .00001, indicating a significant difference between Group 4 and Group 8. For HDL, the t-value is 7.11556 and a p-value < .00001, again indicating a significant difference between the two groups. These results suggest that the treatments have a profound effect on both triglyceride and HDL levels. This effect is due to the pharmacological action of SGLT2 inhibitors. However, in Group 4 & Group 8 blood pressure variation was not significant.

DISCUSSION

As the new definition of metS 2022 given in position paper, apart from the components provided in previous studies; also included are chronic inflammation, hyper-uricemia and sympathetic activation[5]. Patients diagnosed with metS should be considered high cardiovascular risk patients. Implement lifestyle changes along with appropriate treatment [2,3,5]. Progression of metabolic syndrome can be prevented or slowed with early intervention. Consistent with the above, our study also confirms that lifestyle changes are the most important factor in preventing progression, with weight loss and BMI reduction in groups 1 and 5 compared to the other groups. was the most expensive. Most of our dietary changes were similar to those recommended by the 2022 guidelines, including: B. Reducing trans and saturated fat intake may lower triglycerides and increase HDL levels (4). Increasing your fiber intake by eating vegetables, legumes, fruits, and whole grains increases HDL, which helps control blood pressure, weight, and blood sugar levels. Increasing your intake of omega-3 fatty acids and reducing your carbohydrate intake by 50% or more can help reduce triglycerides. Limiting salt intake helps maintain blood pressure. Targeting diseases that contribute to metabolic syndrome is most effective. Diet and exercise are priority modifiable factors for patients with metabolic syndrome [3,5,7].

The Diabetes Prevention Program Research Group conducted a landmark randomized controlled trial that evaluating the efficacy of lifestyle intervention and metformin in preventing type 2 diabetes in pre-diabetes. The study followed more than 3,000 participants with pre-diabetes for an average of 2.8 years and found that lifestyle intervention, such as intensive diet and exercise changes reduced the incidence of type 2 diabetes by 58% compared to placebo. Metformin, a medication commonly reduced the incidence of diabetes by 31% compared to placebo. The study also found that lifestyle intervention were more effective than metformin in preventing the development of metabolic syndrome. This study has had a major impact on diabetes prevention and treatment guidelines, with many healthcare providers recommend lifestyle interventions as the first approach to preventing and treating type 2 diabetes[1]. The HyperGEN study is a family-based study that aimed at investigating the genetic and environmental factors that contribute to the development of hypertension and associated cardiovascular risk factors, including metabolic syndrome. The study followed more than 1,400 people in 19 families for up to 9 years and collected data on a range of cardiovascular risk factors, including blood pressure, lipids, glucose, insulin, and body composition. In this study, both genetic

and environmental factors were significant predictors of metabolic syndrome, and that lifestyle changes, such as weight loss and increased physical activity, were effective in reducing the risk of developing metabolic syndrome. The findings of this study underscore the importance of both genetic and environmental factors in the development of metabolic syndrome and highlight the potential benefits of lifestyle modifications in preventing metabolic syndrome [8].

The MESA study is a multi-center, prospective cohort study that aimed at investigating the association between metabolic syndrome and subclinical cardiovascular disease. The study enrolled 6,800 participants from six different ethnic groups in the United States and collected data on various cardiovascular risk factors, including blood pressure, lipids, glucose, insulin, and body composition. In this study, even in the absence of clinical cardiovascular disease, people with metabolic syndrome develop subclinical cardiovascular disease as measured by measures such as carotid intima-media thickness. The results of this study underscore the importance of identifying and treating metabolic syndrome as a means of reducing the risk of developing cardiovascular disease [9].

The Look AHEAD study was a multicenter, randomized controlled trial that aimed to evaluate the impact of intensive lifestyle interventions on the incidence of cardiovascular disease in overweight and obese individuals with type 2 diabetes. The study included over 5,000 participants and compared the outcomes of those receiving intensive lifestyle interventions (including dietary changes, increased physical activity, and behavioral therapy) to those receiving standard care. The study found that the intensive lifestyle interventions were effective in reducing the incidence of metabolic syndrome and cardiovascular disease in the intervention group, compared to the standard care group[7].

Overall in group 1 and 5 where patients received Lorcaserin + SGLT2 inhibitor and life style modifications all parameters had significant differences when compared with other groups. Whereas in group 3 and 7, no life style modifications were made and there was changes in the parameters seen because of the cumulative effects of Lorcaserin and SGLT2 inhibitors. But for the other four groups (Group 2, 4, 6 and 8) where Lorcaserin was not provided, in group 2, 6 where SGLT2 inhibitors and life style modification there was changes in all parameters except for BMI which had no significant change found. In group 4 and 8 where only SGLT2 inhibitor was given in both with and without mets respectively there were no significant changes in any parameter except for lipemic profile (Triglycerides and HDL) which could be the pharmacological effect of SGLT2 inhibitor itself. The changes in HbA1c and FBS were also not significant which might also consider insulin resistance in obese individuals.

CONCLUSION

Metabolic syndrome is a major health problem that increases the risk of cardiovascular disease and type 2 diabetes. The condition is closely related to lifestyle factors and requires the implementation of lifestyle modifications such as regular exercise and a healthy diet are effective in reducing the risk of developing metabolic syndrome and its associated complications. Further research is needed to fully understand the underlying mechanisms of metabolic syndrome and to develop more effective treatments for this condition. Studies have shown that lifestyle modifications such as diet and exercise can help improve risk factor for metabolic syndrome and help to reduce the risk of cardiovascular disease and diabetes. However, the most effective type of lifestyle modification may vary depending on individual factors, so it is important to work with a healthcare provider to tailor the best approach for each patient.

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