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Original Article

Efficacy of Metformin plus Sodium Glucose Transporter-2 inhibitors (SGLT-2i) in Obese Type 2 Diabetic patients at Liaquat University Hospital Hyderabad/Jamshoro

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Abstract

Objective: To determine the efficacy of Metformin plus SGLT2 inhibitors in type 2 obese diabetic patients attending OPD at Liaquat University Hospital Hyderabad / Jamshoro.

Methods: This quasi-experimental study was undertaken in the out-patient department of Liaquat University Hospital Hyderabad / Jamshoro from June 10th, 2022 to February 10th, 2023. All patients with type 2 DM for at least 8 months duration, already taking metformin with BMI ≥30kg/m2 and age limit from 30-55 years, of either gender were consecutively enrolled. SGLT2 inhibitors 10 mg once daily was added to Tab Metformin 500mg. The reduction in HbA1c of at least ≥0.5% from the baseline, at 6 months was considered as efficacy.

Results: Of 114 patients, the mean age was 45.24 ±4.89 years. There were 76 (66.7%) males and 38 (33.3%) females. The mean weight, height, and BMI of the patients were 87.51 ±9.33 kg, 1.54 ±0.06 m, and 32.04 ±2.64 kg/m2 respectively. The mean pre and post HbA1c level were 9.78 ±1.43 and 8.73 ±1.39 respectively. 70 patients (61.4%) have shown reduction of HbA1c from 0.5 to 1.5% in 6 months, p-value was 0.002 significant in those with high A1c. Weight reduction was significant in both groups, BMI <30 p value 0.03 and in those BMI >30, p value was 0.02.

Conclusion: The efficacy of Metformin plus SGLT2 inhibitors was found in more than half of the type 2 obese diabetic patients attending OPD at Liaquat University Hospital Hyderabad / Jamshoro.

Keywords: Efficacy, Metformin, SGLT2 Inhibitors, Type 2 Diabetes, Obesity

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Introduction

Diabetes mellitus type 2 is a clinical syndrome which encroaches any system of the body due to hyperglycemia and derangements of counter regulatory hormones. Due to the nature of this disease and high prevalence, Diabetes mellitus type 2 is projected as a big public problem.[1] The holistic approach is patient centered, used to treat type 2 diabetes, such as lifestyle modifications, self-blood glucose monitoring, and education about complications. The treatment includes oral antidiabetic drugs, insulin and insulin like agents; GLP1 agonists.

However, an alternative, more intensive approach is initial combination treatment. Recently societies emphasized patient's Glycated hemoglobin (HbA1c) <7% for which initial combination therapy should be considered. Type 2 diabetes accounts for more than two third of cases among all diabetic subjects. The major problem is resistance to insulin or blunt response of insulin. The obesity is the main culprit of type 2 diabetes. Hence, if a diabetic patient will lose about 10% of body weight, remission from diabetes is possible. This overall reduces the associated cardiovascular events like fatal and non-fatal myocardial infarction.[2]

The proportion of people with type 2 diabetes is increasing in most countries, 79% of adults with diabetes are living in low and middle-income countries. The greatest

number of people with diabetes were between 40 and 59 years of age. As reported by International Diabetes Federation, recently, in Pakistan every 3rd individual is suffering from Diabetes and more than 30 million people have diabetes.[3] The high prevalence in Pakistan is contributed by life style, genetics, western diet, early obesity, lack of motivation for taking natural diet and high sugar intake.

World health organization has shown the high prevalence of obesity in Pakistan (58 -64% in adults). The females are more obese than males.[4] So obesity and diabetes are linked tightly. New drugs like SGLT2 inhibitors and Glucagon like peptide receptor agonists 1 (GLP-1) are unique to reduce cardiovascular mortality and morbidity. SGLT2 inhibitors are exceptionally well in patients of diabetic kidney disease. Over all these drugs are beneficial in reduction of total body weight also.[5] SGLT2 inhibitors block reabsorption of glucose in the proximal convoluted tubule and cause natriuresis and glycosuria. The net effect is reduced weight and blood pressure along with control of diabetes[6].

One recent study has shown SGLT-2 inhibitors achieved better glycemic control and greater weight reduction than DPP4 inhibitors without increasing the risk of hypoglycemia in patients with T2DM that is inadequately controlled with insulin.[7] More data has shown that SGLT2 inhibitor was associated with a significant increase in HDL after 6 months of use in patients with type 2 diabetes compared with those with DPP-4 inhibitors.[8] SGLT2 inhibitors reduce 1.5–2 kg weight while the reduction for GLP1-Ras is 2–4 kg, and if both are combined, that will be 3–5 kg.[9]

The rationale of this study is to observe potential benefits of Metformin plus SGLT2 inhibitors apart from glycemic control such as reduction in weight, reduction in HbA1c and glycemic control in our population so that the patients can be properly rationalized and managed according to the findings of the study to prevent the patients from developing life-threatening complications due to type 2 Diabetes Mellitus.

Methods

This study was started after approval of ethical review committee of Liaquat University of Medical and Health Sciences Jamshoro, Sindh, Pakistan with reference no LUMHS/REC/-29 DATED 9.2.21. The patients attending diabetic /medical OPDs of Liaquat university hospital fulfilling the inclusion criteria were registered in the study. The purpose, procedure, risks and benefits were explained, and written consent was taken from patients on proforma written in Urdu and Sindhi. The duration of study was June 10th, 2022 to February 10th, 2023 and sampling technique was non-probability consecutive. The required sample size calculated using open Epi was 114 obese T2DM patients.

Inclusion criteria

- All patients with type 2 DM for at least 8 months duration, already taking Tab Metformin.
- Obese individuals (BMI ≥30kg/m^2).
- Age from 30-55 years of either gender.

Exclusion criteria

- Patients already on insulin.
- Patients with end stage renal disease on dialysis.
- Patients with inflammatory conditions; i.e., with raised CRP levels.
- Patients with frequent urinary tract infections.
- Patients with other endocrinopathies like Thyroid, Addison's disease.
- Female patients with pregnancy.

The data was collected on pre-designed proforma including age, gender, and duration of diabetes. Baseline HBA1c level was noted, and the height of the patient was measured on wall mounted scale in centimeters without shoes and cap. The weight was measured on electronic weighing machine without shoes and in light clothes in kg. The BMI was calculated by dividing the weight in kg with height in m^2. The base line BMI was 30 in either sex. The HBA1C was measured by HPLC8 Analyzer. 2cc blood was drawn with full aseptic technique from accessible vein and send to nearby laboratory, diagnostic lab LUMHS. Two HbA1c samples were obtained, at 3 and 6 months of SGLT2 treatment.

SGLT2 inhibitors 10mg (Empagliflozin or Dapagliflozin) once daily was added to Tab Metformin 500mg once daily. Free drug samples were arranged by authors with help of pharmaceutical companies and discounted coupons were also given to remote patients for 6 months. Patients were followed at 3 months and finally at 6 months after the initiation of combination treatment by estimation of BMI and HbA1c. The reduction in HbA1c of at least ≥0.5% from the baseline, at 6 months was considered to be efficacious. This information along with demographics and other details as mentioned above was noted in the proforma attached as annexure.

Data analysis procedure

The data was analyzed by using SPSS version 22. The categorical variables such as gender, marital status, residence, occupational status, education level and efficacy were computed as numbers and percentages. Normality of data was assessed by using Shapiro wilk test and the numerical data such as age, height, weight, BMI, baseline HbA1C, family monthly income and duration of diabetes were computed as mean and standard deviation or median (IQR) on the basis of normality.

The stratification was done for age, gender, residence, occupational status, education level and duration of diabetes. The pre and post stratification done by paired student t test was applied before and after SCLT2 and the P-value ≤ 0.05 was considered as statistically significant.

Results

Of 114 patients, the mean age of the patients was 45.24 ±4.89 years. There were 60 (52.6%) patients with ≤ 45 years and 54 (47.4%) with >45 years of age. Gender distribution showed that 76 (66.7%) were males and 38(33.3%) females. The mean weight, height, and BMI of the patients were 87.51 ±9.33 kg, 1.54 ±0.06 m, and 32.04 ±2.64 kg/m2 respectively (Table 1).

Table 1: *Demographic characteristics of 114 patients*

Variable		Mean/ Number	S D	Percentage
Gender	MALE	76		66.7%
	FEMALE	38		33.3%
BMI	<30 kg/m^2	54		47.4%
	>30 kg/m^2	60		52.6%
Mean duration of diabetes (month)		8.09	±1.91	
Duration of diabetes (month)	< 9 months	74		64.9%
	> 9 months	40		35.1%
Age		45.24	±4.89	
Hba1c		9.78	±1.43	
Married		54		47.4%
Unmarried		60		52.6%
No education		36		31.6%
Educated		78		68.42%

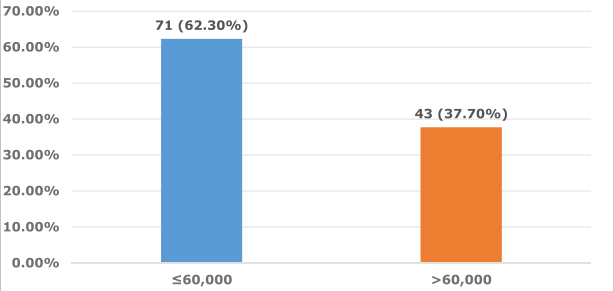

Chart 1: Family income of the patients, rupees (n=114)

There were 54 (47.4%) patients with ≤30 kg/m2 and 60 (52.6%) with >30 kg/m2 of BMI. The mean family income of the patients was 58,710 ±17,582 rupees, 71 (62.3%) patients with ≤60,000 rupees and 43 (37.7%) with >60,000 rupees family income (Chart 1).

The mean duration of diabetes was 8.09 ±1.91 months, 74 (64.9%) patients with ≤ 9 months and 40 (35.1%) with >12 months of duration of diabetes.

54 (47.4%) patients were married and 60 (52.6%) were unmarried (Table1).

Regarding residential status rural residence was observed in 83 (72.8%) and urban residence in 31 (27.2%) patients. Employment status was observed in 30(26.3%) patients.

No education was observed in 36 (31.6%) patients, 52 (45.6%) with less than equal to matric qualification and 26 (22.8%) with more than equal to intermediate status.

The income was divided into 2 groups and no significant difference in efficacy of SGLT2 was noted in relation to income status (Table 2).

The mean pre and post HbA1c level were 9.78 ±1.43 and 8.93 ±1.39 respectively (Table1).

The HbA1c reduction results were as follows; 70 patients (61.4%) showed 0.7 %, - 1.55% - 2, 2%, p value 0.002 (Table 3).

Patients were divided in two groups on basis of BMI, <30 and >30. With addition of SGLT inhibitor, both groups have shown significant reduction of weight, p value was 0.01 in <30 and p value 0.02 in patients >30 BMI. The weight reduction was 0.5 -1 kg and in 6 months maximum weight reduction was 1.5 kg in patients BMI < 30. There was a significant reduction seen at 3 and 6

Table 2: *Income Distribution*

Family income, rupees	Efficacy		Total	p-value
	Yes	No		
[illegible]	44 (62.0)	27(38.0)	71(100)	0.107
>60,000	20 (46.5)	23(53.5)	43(100)	
Total	64 (56.1)	50(43.9)	114(100)	

Table 3: *Serial HbA1c after addition of SGLT2 inhibitors in 114 patients*

Number of Patients -A1c	HbA1C		p-value
	0&3months	6months	
30	9	7.8	0.01
40	10.5	8.7	0.002
44	7.5	7.2	1.1

Table 4: *Table 4: Comparison of efficacy of SGLT2 combination on weight (n=114)*

BMI	Efficacy		Total	p-value
	Yes	No		
≤30	20	34	54	0.01
>30	45	15	60	0.02
Total	65	49	114	

months in 42% patients with BMI> 30 (Table 4)

Discussion

This study is unique and conducted first time in this region of the province to see effects of combination of metformin and SGLT2 inhibitors on weight and HbA1c level.

Still majority of diabetic societies are recommending Metformin is the drug of choice when atherosclerotic cardiovascular risk is low along with life style modification.[10] When type 2 diabetes is associated with cardiovascular risk then choices are SGLT2 inhibitor and GLP 1 receptor agonists. Both these agents are superior to metformin in cardiovascular benefits.[11] When there is less frailty and patient is well kept then HbA1c targets will require to be tightly controlled to 7%. By adding DPP4 or SGLT2 inhibitor, HbA1c target is achieved and this combination is further potentiated by addition of metformin[12]. SGLT2 inhibitors are more beneficial for cardio and reno-protection in type 2 diabetes.[13]

A recent large trial mentioned that the hypoglycaemic efficacy and weight reduction by SGLT2 inhibitors are comparatively more in Asian descent than other population.[14] The combination therapy of patients with T2DM accelerates reduction in HbA1c when SGLT2i is added.[15] Our study has analysed combination of two different classes of anti-diabetic drugs including metformin and SGLT2 inhibitors. There was no fear of hypoglycaemia in this combination as reported By Ibrar et al that even in Ramadan this combination was the safest.[16]

There is no difference statistically between income and the efficacy of combination and this is stated in our study that any group earned less than or more than 60,000 Pakistani rupees did not show a significant difference. This result of our study did not match a recent study of China that showed 0.5% difference in HbA1c in people earning 10 thousand Yan and those who earned less than 10 thousand.[17] Recent clinical evidence shows that SGLT2 inhibitors is an effective combination for T2DM treatment, providing HbA1c reductions of 1.1 to 1.5%, and weight reductions of approximately 2 kg when added to metformin, which is its primary place in therapy.[18] These results are comparable to our study where patients have shown reduction of weight 0.5 to 1.5 kg in both groups either BMI < 30 or > 30.

When SGLT2i was added to metformin, the weight decreased > 2 Kg in 24 weeks and > -1 %decrease in the total fat mass.[19] The change in HbA1c, one of the second endpoints of the study, was a 0.45 % reduction in the patients using metformin with SGLT2i, which was similar to Hong et al.'s study indicated 0.42 % HbA1c reduction in 6 months[20]. This also matched with our study and HbA1c has been reduced progressively from 3 to 6 months from 0.5 to 2.2 % and p value was statically significant 0.002.

One study showed three drug groups based on their efficacy in weight loss; metformin or acarbose, empagliflozin and GLP 1 receptor agonist, resulted in weight loss < 3.2% initially. Empagliflozin induced weight loss 3.2% - 5%. GLP 1 receptor agonists resulted in a weight loss > 5%[21] and this was also supported in our study where the weight loss was up to 2 kg after 6 months and maximum observed in high BMI.

Conclusion

This study was conducted in a controlled population and showed encouraging results of combination of metformin and SGLT2 inhibitors. Our study concluded that weight loss and HbA1c are two main factors in type 2 diabetes and this combination has impressive efficacy. It is better to start with this combination even those who have less risk of cardiovascular disease.

Conflict of Interest: *None*

Funding Source: *None*

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