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Diabetology

RETROSPECTIVE, OBSERVATIONAL, NON-INTERVENTIONAL ANALYSIS OF NON-GLYCEMIC PARAMETERS WITH SGLT2I ON TYPE 2 DIABETES MELLITUS PATIENTS STABLE ON OADS

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ABSTRACT

BACKGROUND: Sodium glucose co-transporter 2 inhibitors (SGLT2I) have been shown to have extra-glycemic beneficial effects for type 2 diabetic patients.

OBJECTIVE: The objective of the study was to see the degree of changes of body parameters with degree change in HbA1c over 12 weeks and also find out the drug causing maximum changes in parameters after 12 weeks. This is a retrospective, observational, and single arm study. Thirty three T2DM patients matching the inclusion criteria and using SGLT2I (dapagliflozin, empagliflozin, and canagliflozin) were included for the study. Both glycemic parameters (Changes in HbA1c) and non-glycemic parameters (changes in BMI, total subcutaneous fat, total visceral fat, skeletal muscle of trunk, and waist circumference) were measured in the cases at baseline and after 12 weeks. Data was analyzed by SPSS version 21. P value < 0.05 was considered statistically significant.

RESULTS: Out of the 33 patients, 17 (51.50%) were male and 16 (48.5%) were female. There was a significant reduction in the overall mean levels of HbA1c% (p=0.014), Visceral Fat (p=0.0027), and Waist Circumference (p=0.012) after 12 weeks. Multiple regression analysis revealed that change in HbA1c was influenced by baseline BMI, visceral fat, skeletal muscle trunk, HbA1c but was not influenced by changes in other parameters and duration of diabetes.

CONCLUSION: Different SGLT2I affect the non glycemic parameters like visceral fat and waist circumference change in T2DM patients independent of changes in HbA1c. Also, the three classes of SGLT2I used in the study had similar effects on the changes in glycemic as well as non glycemic parameters.

KEYWORDS :

INTRODUCTION

Type 2 diabetes mellitus is a chronic metabolic disorder that is associated with suboptimal blood sugar control, insulin resistance, and multiple other pathological changes. The worldwide incidence of diabetes mellitus is 1 in every 11 adults (9.1%) and 90% of these adults with diabetes mellitus have type 2 diabetes mellitus (1). Metformin is the first line of treatment for type 2 diabetes mellitus. Sodium glucose co-transporter 2 inhibitors (SGLT2I) are the second line of therapy for type 2 diabetic patients (2). There are several co morbidities associated with type 2 diabetes mellitus like hypertension, obesity, cardiovascular disorders, retinal degeneration, etc. SGLT2I have helped in the treatment and management of type 2 diabetic patients because of their various roles in not only managing or controlling the blood sugar levels but also providing extra-glycemic benefits (3). These molecules through their novel insulin sparing action bring out sugar through urine and thus cause calorie loss as well as loss of visceral fat which thereby reduces insulin resistance (4, 5).

The SGLT2 is an active enzyme that is abundantly expressed in the renal proximal tubules. The most important function of SGLT2 is the reabsortion glucose. SGLT2 reabsorbs 80% to 90% of glucose in the renal proximal tubules thereby diverting the glucose back into circulation. So, inhibition of SGLT2 can reduce blood glucose levels by insulin independent mechanism. The inhibition of SGLT2 by SGLT2I have been reported to have positive effects on the type 2 diabetes mellitus associated co morbidities like hypertension and obesity, besides maintaining glycemic control (6, 7). Several studies have reported the extra-glycemic effects of SGLT2I in type 2 diabetes mellitus patients. These inhibitors of SGLT were observed to decrease the glycemic parameters like HbA1c, fasting plasma glucose levels, and body weight. The basic mechanism proposed for these extra-glycemic effects of SGLT2I is glucosuria that involves loss of calories through urine (8-11).

All types of SGLT2I have the potential to bring out sugar out of urine causing calorie loss as well as visceral fat loss. Hence in this study this property was used to test the hypothesis that these drugs might also affect the total visceral fat percentage, BMI, waist circumference and thereby help attain extra-glycaemic benefits to these type 2 diabetics. This property seems to be a class effect and we have looked into the data to find out the drug causing maximum changes in parameters after 12 weeks after adjusting for age, duration of diabetes and co-existent drugs causing changes in visceral parameters. This study addresses the changes seen with SGLT2I in T2DM patients who are already stable on oral diabetic drugs (OADs) or any other drugs for existing co-morbidities after 12 weeks of therapy.

MATERIALS AND METHODS

Study population

This is a retrospective, observational, and single arm study. Thirty three T2DM patients matching the inclusion criteria were included for the study. The inclusion criteria were: Type 2 diabetes mellitus patients put on any dose and type of SGLT2I with any HbA1c level, eGFR >/= 45 ml/min/1.73 sq.m, patients stable on prior OADs for more than 2 weeks (no history of SGLT2I use in prior 3 months), patients on pioglitazone (minimum period on pioglitazone for more than 6 months prior to inclusion, no insulin of any variety or any other injectable drugs, on standard treatment for all other existing chronic diseases on stable doses, no weight loss medications other than standard protocol of aerobic exercises of fixed duration, and no dose titration for pioglitazone or addition of any other medicines that might change the body parameters.

Study Assessments

All the patients were physically examined for vitals such as pulse, blood pressure, respiratory rate, and weight. Systemic examination of cardiovascular system, central nervous system and abdomen was carried out for all the patients. The GTI seen with SGLT2I is actually easily treatable by simple standard antifungal regimes.

Parameters measured at baseline and after 12 weeks

Both glycemic parameters (Changes in HbA1c) and non-glycemic parameters (changes in BMI, total subcutaneous fat, total visceral fat, skeletal muscle of trunk, and waist circumference) were measured in the cases at baseline and after 12 weeks. The visceral fat and body parameter assessment was done using Omron HBF 375 Karada scan which has been used in many other studies and the instructions were followed for measurement as given in the leaflet of the machine.

Statistical analysis

Data was analyzed by SPSS version 21. Continuous data were represented as mean±SD and categorical data were represented as n (%). Frequencies/percentages were calculated for qualitative variables and compared between groups through Chi Square test. The parameters at baseline were compared with the parameters after 12 weeks by paired t-test (for two groups) and ANOVA (for more than two groups). P value < 0.05 was considered statistically significant. Pearson's correlation coefficient was calculated to find any correlation between baseline parameters with the changes in the parameters after 12 weeks and between changes in different parameters. Linear regression analysis was done to find out the factors influencing the changes in parameters.

RESULTS

The present study included 33 T2DM patients. Out of the 33 patients, 17 (51.50%) were males and 16 (48.5%) were females. There was no significant difference in the gender distribution (Chi-square=0.03, p=0.86). In the present study, the patients used *Dapagliflozin* (n=12/33), *Empagliflozin* (n=5/33), and *Canagliflozin* (16/33) as SGPT2I.

The mean age of the patients was 54.61±12.15 years. The mean duration of diabetes was 8.47±5.43 years. The mean baseline %HbA1c was 8.02±2.06. The baseline characteristics of the patients are listed in Table 1. There was a significant reduction in the overall mean levels of HbA1c% (p=0.014), Visceral Fat (p=0.0027), and Waist Circumference (p=0.012) after 12 weeks. There were no significant changes seen in the overall means of parameters like BMI, total fat, and skeletal muscle trunk after 12 weeks (Table 2). HbA1c%, Visceral Fat, and Waist Circumference was reduced in 21(63.64%), 21(63.64%), and 22(66.67%) patients respectively (Table 3).

Table 1: Baseline patient characteristics.

N=33	Mean±SD, n%
Duration of diabetes (Years)	8.47±5.43
Gender	17 (51.50%) males, 16 (48.5%) females
Age (Years)	54.61±12.15
BMI (kg/m^2)	27.99±3.73
Total fat	35.188±6.11
Visceral fats	14.55±4.58
Skeletal muscle trunk	17.09±3.30
Waist circumference	99.00±7.78
HbA1C%	8.018±2.06

Table 2: Changes in parameters after 12 weeks.

Parameters	Baseline	12 weeks	t value	p value	95%(CI)
BMI	28.00±3.72	27.71±4.00	1.39	0.17	[-0.12, 0.69]
Total Fat	35.18±5.97	35.40±6.37	0.51	0.61	[-1.08, 0.65]
Visceral Fat	14.54±4.57	13.40±4.57	3.24	0.0027	[0.42, 1.85]
Skeletal Muscle Trunk	17.09±3.27	17.22±3.42	0.70	0.48	[-0.50, 0.24]
Waist Circumference	99.00±7.77	97.48±8.36	2.66	0.012	[0.35, 2.67]
HbA1c	8.02±2.06	7.20±1.08	2.57	0.014	[0.17, 1.46]

Table 3: Frequency of changes in parameters.

	Reduction in total population n (%)	Increase in total population n (%)	No change in total population n (%)
BMI	21(63.64%)	11(33.33%)	1(3.03%)
Total Fat	15(45.45%)	17(51.52%)	1(3.03%)
Visceral Fat	21(63.64%)	7 (21.21%)	5(15.15%)
Skeletal Muscle Trunk	11(33.33%)	20(60.61%)	2(6.06%)
Waist Circumference	22(66.67%)	10(30.30%)	1(3.03%)
HbA1c	21(63.64%)	12(36.36%)	0(0%)

Out of the patients who showed reduction in HbA1c%, 71.43%, 76.19%, and 71.43% also showed reduction in Visceral Fat, BMI, and Waist Circumference respectively and 61.90% patients showed an increase in skeletal muscle trunk. Out of the patients who showed reduction in Visceral Fat, 71.43%, 85.71%, and 76.19% showed reduction in HbA1c, BMI, and Waist Circumference respectively and 61.90% patients showed an increase in skeletal muscle trunk. Out of the patients who showed reduction in Waist Circumference, 72.73%, 68.18%, and 77.27% showed reduction in Visceral Fat, HbA1c, and BMI respectively and 63.64% patients showed an increase in skeletal muscle trunk (Table 4).

Table 4: Combined frequency of changes in parameters.

	Reduction in Waist Circumference (n=22)	Reduction in BMI (n=21)	Reduction in HbA1c (n=21)	Reduction in Visceral Fat (n=21)	Increase in Skeletal Muscle Trunk (n=20)
Increase in Skeletal Muscle Trunk	63.64%	61.90%	61.90%	61.90%	
Reduction in Visceral Fat	72.73%	85.71%	71.43%		65%
Reduction in HbA1c	68.18%	76.19%		71.43%	65%
Reduction in BMI	77.27%		76.19%	85.71%	65%
Reduction in Waist Circumference		80.95%	71.43%	76.19%	70%

Patients were categorized into three groups on the basis of their baseline HbA1c levels. Twenty four patients (72.70%) had 6.00 to 7.90%, 2 patients (6.10%) had 8 to 10%, and 7 patients (21.20%) had >10% baseline HbA1c level. There was no significant difference in the mean reduction in BMI, visceral fat, and waist circumference, and increase in skeletal muscle trunk between the groups (Table 5).

Table 5: Comparison of changes in parameters between patient groups on the basis of baseline HbA1c%.

Parameters	HbA1c (6-8%) (n=24)	HbA1c (8-10%) (n=2)	HbA1c (>10%) (n=7)	Overall p value
Reduction in BMI	14(58.33%); 0.94±1.27	2(100%); 0.25±0.21	5(71.43%); 0.78±0.31	0.70
Reduction in Visceral Fat	14(58.33%); 1.5±1.3	2(100%); 3.5±3.5	5(71.43%); 3.4±1.98	0.07
Increase in Skeletal Muscle Trunk	15(62.50%); -0.66±0.63	1(50%); -0.90	4(57.14%); -1.03±0.95	0.64
Reduction in Waist Circumference	17(70.83%); 2.71±1.31	2(100%); 8.50±7.78	3(42.16%); 2.00±1.73	0.007

Baseline parameters were correlated with change in parameters, and change in parameters were correlated with change in other parameters. Baseline HbA1c% did not correlate with changes in any other parameters. Change in HbA1c% also did not correlate with change in any other parameters (Table 6A-6G). Baseline waist circumference positively correlated (r=0.36, p=0.04) with change in skeletal muscle trunk and negatively correlated with change in skeletal muscle trunk. Change in BMI positively correlated with change in waist circumference (r=0.42, p=0.02), change in total fat correlated negatively with change in skeletal muscle percentage of trunk (r=-0.91, p<0.0001), and change in visceral fat correlated positively with change in waist circumference (r=0.36, p=0.04).

Table 6A: Correlation between baseline BMI level with change in other parameters

	r value	p value	95% CI
Δ T Fat	-0.31	0.08	[-0.59, 0.04]
Δ V Fat	-0.02	0.91	[-0.36, 0.33]
Δ Skeletal muscle trunk	0.30	0.08	[-0.04, 0.59]
Δ waist circumference	-0.31	0.07	[-0.59, 0.34]
ΔHbA1C	-0.01	0.97	[-0.35, 0.34]

Pearsons's correlation coefficient (r) was calculated to find any correlation between parameters. P value<0.05 was considered significant. Δ=change.

Table 6B: Correlation between baseline Total Fat with change in other parameters

	r value	p value	95% CI
Δ BMI	-0.08	0.64	[-0.41, 0.27]
Δ V Fat	0.06	0.74	[-0.29, 0.40]
Δ Skeletal muscle trunk	-0.05	0.79	[-0.38, 0.30]
Δ waist circumference	-0.32	0.07	[-0.59, 0.32]
ΔHbA1C	0.22	0.21	[-0.13, 0.53]

Pearsons's correlation coefficient (r) was calculated to find any correlation between parameters. P value<0.05 was considered significant. Δ=change.

Table 6C: Correlation between baseline Visceral Fat with change in other parameters

	r value	p value	95% CI
Δ BMI	-0.15	0.64	[-0.47, 0.21]
Δ T Fat	-0.27	0.74	[-0.56, 0.08]
Δ Skeletal muscle trunk	0.17	0.79	[-0.18, 0.49]

Δ waist circumference	-0.05	0.07	[-0.39, 0.30]
ΔHbA1C	0.003	0.21	[0.34, 0.35]

Pearsons's correlation coefficient (r) was calculated to find any correlation between parameters. P value<0.05 was considered significant. Δ=change.

Table 6D: Correlation between baseline Skeletal muscle trunk with change in other parameters

	r value	p value	95% CI
Δ BMI	0.10	0.61	[-0.26, 0.42]
Δ T Fat	0.03	0.86	[-0.32, 0.37]
Δ VFat	-0.17	0.35	[-0.48, 0.19]
Δ waist circumference	0.16	0.39	[-0.21, 0.47]
ΔHbA1C	-0.29	0.10	[-0.57, 0.06]

Pearsons's correlation coefficient (r) was calculated to find any correlation between parameters. P value<0.05 was considered significant. Δ=change.

Table 6E: Correlation between baseline waist circumference with change in other parameters

Δ T Fat	-0.45	0.008	[-0.69, -0.13]
	r value	**p value**	**95% CI**
Δ BMI	-0.01	0.94	[-0.35, 0.33]
Δ VFat	0.03	0.85	[-0.31, 0.37]
Δ Skeletal muscle trunk	0.36	0.04	[0.02, 0.63]
ΔHbA1C	-0.21	0.27	[0.51, 0.16]

Pearsons's correlation coefficient (r) was calculated to find any correlation between parameters. P value<0.05 was considered significant. Δ=change.

Table 6F: Correlation between baseline HbA1C with change in other parameters

	r value	p value	95% CI
Δ BMI	0.03	0.88	[-0.32, 0.37]
Δ T Fat	0.13	0.47	[-0.22, 0.45]
Δ VFat	0.27	0.13	[-0.08, 0.56]
Δ skeletal muscle trunk	-0.11	0.70	[-0.40, 0.28]
Δwaist circumference	-0.21	0.29	[-0.50, 0.16]

Pearsons's correlation coefficient (r) was calculated to find any correlation between parameters. P value<0.05 was considered significant. Δ=change.

Table 6G: Comparison of baseline and changes in glycemic and non glycemic parameters in different SGLT2I groups

	N		Mean	Std. Deviation	95% Confidence Interval for Mean		Minimum	Maximum	P value
					Lower Bound	Upper Bound			
Gender	1	12	1.58	.515	1.26	1.91	1	2	
	2	5	1.40	.548	.72	2.08	1	2	0.71
	3	16	1.44	.512	1.16	1.71	1	2	
Age	1	12	52.00	14.149	43.01	60.99	27	71	
	2	5	52.40	14.993	33.78	71.02	32	72	0.49
	3	16	57.25	9.664	52.10	62.40	38	71	
B. BMI	1	12	28.46	5.126	25.20	31.72	23	41	
	2	5	26.52	2.698	23.17	29.87	24	30	0.63
	3	16	28.11	2.738	26.65	29.57	23	34	
FU. BMI	1	12	28.15	5.431	24.70	31.60	22	42	
	2	5	26.12	2.417	23.12	29.12	24	30	0.63
	3	16	27.88	3.157	26.20	29.56	24	35	
ch BMI	1	12	.31	.511	-.02	.63	-1	1	
	2	5	.40	.914	-.73	1.53	0	2	0.96
	3	16	.23	1.563	-.61	1.06	-2	5	
B. TOTAL FAT	1	12	36.425	5.1321	33.164	39.686	28.4	43.3	
	2	5	31.680	8.3736	21.283	42.077	22.1	42.4	0.34
	3	16	35.356	5.7270	32.305	38.408	25.4	46.6	
FU. TOTAL FAT	1	12	36.317	5.3939	32.890	39.744	26.6	42.9	
	2	5	31.300	8.5680	20.661	41.939	22.1	40.4	0.30
	3	16	36.006	6.2450	32.678	39.334	25.9	48.0	
ch T FAT	1	12	.108	2.0991	-1.225	1.442	-4.9	2.8	
	2	5	.380	2.8674	-3.180	3.940	-2.5	4.4	0.62
	3	16	-.650	2.6389	-2.056	.756	-7.1	4.7	
B. VISCERAL FAT	1	12	14.54	5.659	10.95	18.14	8	29	
	2	5	11.10	1.746	8.93	13.27	10	14	0.16
	3	16	15.63	3.897	13.55	17.70	9	22	
FU. VISCERAL FAT	1	12	13.21	5.553	9.68	16.74	7	29	
	2	5	10.60	.742	9.68	11.52	10	12	0.26
	3	16	14.43	4.197	12.19	16.66	8	22	
chvisFAT	1	12	1.33	1.801	.19	2.48	-1	5	
	2	5	.50	1.173	-.96	1.96	-1	3	0.74
	3	16	1.20	2.410	-.08	2.48	-3	6	
B. SKELETAL MUSCLE TRUNK	1	12	16.36	2.530	14.75	17.97	12	20	
	2	5	19.56	5.100	13.23	25.89	13	26	0.17
	3	16	16.87	2.943	15.30	18.44	11	22	
FU. SKELETAL MUSCLE TRUNK	1	12	16.450	2.6238	14.783	18.117	13.0	21.1	
	2	5	20.060	5.2300	13.566	26.554	13.8	25.9	0.12
	3	16	16.913	3.0694	15.277	18.548	11.3	21.7	
chSKETR	1	12	-.092	.9298	-.682	.499	-1.6	1.8	
	2	5	-.500	1.2247	-2.021	1.021	-2.4	.9	0.71
	3	16	-.044	1.1343	-.648	.561	-2.4	2.0	
B. WAIST CIRCUMFERENCE	1	12	98.08	8.129	92.92	103.25	80	114	
	2	5	95.20	4.207	89.98	100.42	91	101	0.33
	3	16	100.88	8.164	96.52	105.23	86	110	

FU. WAIST CIRCUMFERENCE	1	12	97.00	9.516	90.95	103.05	79	115	
	2	5	92.80	4.604	87.08	98.52	88	100	0.32
	3	16	99.31	8.130	94.98	103.64	86	112	
chWCIR	1	12	1.08	2.193	-.31	2.48	-2	4	
	2	5	2.40	1.140	.98	3.82	1	4	0.76
	3	16	1.56	4.305	-.73	3.86	-3	14	
B. HbA1C	1	12	8.908	2.6113	7.249	10.567	6.2	14.4	
	2	5	7.100	.7000	6.231	7.969	6.2	7.9	0.15
	3	16	7.638	1.6958	6.734	8.541	6.6	12.4	
FU. HbA1c	1	12	7.667	1.4431	6.750	8.584	6.1	10.6	
	2	5	6.720	.6870	5.867	7.573	6.2	7.9	0.16
	3	16	7.000	.7554	6.597	7.403	5.8	8.7	
chHbA1C	1	12	1.242	2.3998	-.283	2.766	-.4	7.8	
	2	5	.380	.6058	-.372	1.132	-.3	1.2	0.61
	3	16	.638	1.5966	-.213	1.488	-.9	5.9	
Duration of diabetes	1	12	6.79	4.887	3.69	9.90	1	15	
	2	5	8.20	4.382	2.76	13.64	4	15	0.36
	3	16	9.81	6.014	6.61	13.02	2	24	

Multiple regression analysis revealed that change in HbA1c was influenced by baseline BMI, visceral fat, skeletal muscle trunk, HbA1c but was not influenced by changes in other parameters and duration of diabetes (Table 7, 7B). Change in visceral fat was influenced by age, gender, baseline BMI, baseline visceral fat, and change in skeletal muscle trunk. Change in waist circumference was influenced by baseline total fat, baseline skeletal muscle trunk, and change in BMI. Table 6 describes the frequency of users of SGLT2I on the basis of type of SGLT2I used. The three types of SGLT2I used by the patients were *Dapagliflozin* (36.36%), *Empagliflozin* (15.15%), and *Canagliflozin* (48.48%). When the patients using different types of SGLT2I were compared, it was observed that there was no significant difference in the changes in different body parameters and HBA1c% among the groups of patients using different types of SGLT2I.

Table 7A: Regression analysis of change in HbA1c% with baseline parameters

Coefficientsa						
Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	10.605	8.695		1.220	.235
	Gender	-1.237	.634	-.344	-1.950	.063
	Age	.030	.022	.199	1.380	.181
	B. BMI	.345	.138	.704	2.494	.020
	B. Total Fat	-.244	.130	-.797	-1.873	.074
	B. Visceral Fat	-.283	.092	-.710	-3.070	.005
	B. Skeletal muscle trunk	-.568	.233	-1.018	-2.443	.023
	B. Waist Circumference	-.027	.037	-.115	-.724	.476
	B. HbA1C	.753	.082	.851	9.189	.000
	D/ Diabetes	-.021	.032	-.063	-.662	.514
a. Dependent Variable: chHbA1C. B=Baseline.						

Table 7B: Regression analysis of change in HbA1c% with change in other parameters

Coefficientsa						
Model		Unstandardized Coefficients	Standardized Coefficients		t	Sig.
		B	Std. Error	Beta		
1	(Constant)	-1.107	2.625		-.422	.677
	Gender	.602	.821	.167	.733	.471
	Age	.031	.034	.205	.898	.378
	ch BMI	.460	.329	.292	1.398	.175
	ch T FAT	.498	.404	.667	1.232	.230
	chvisFAT	.189	.220	.209	.859	.399
	chSKETR	.781	.884	.451	.884	.386
	chWCIR	-.030	.150	-.053	-.197	.845
	D/ Diabetes	-.087	.069	-.259	-1.271	.216
a. Dependent Variable: chHbA1C. Ch=Change.						

DISCUSSION

Type 2 diabetes mellitus is a chronic metabolic disease that affects almost all age groups (as per epidemiological data). Being a metabolic disorder, type 2 diabetes mellitus is primarily associated with other comorbidities. The most important type 2 diabetes mellitus associated comorbidities are obesity (12), dyslipidemia (13), non alcoholic fatty liver (14), hypertension (15), chronic kidney disease (16), cardiovascular diseases (17), depression (18), sleep disorders (19), and cancer (20). Most adults with diabetes have at least one comorbid chronic disease.

The risks of developing comorbidities in type 2 diabetes mellitus can be reduced by adopting healthy lifestyle. Healthy lifestyle in the context of managing type 2 diabetes mellitus includes a plethora of practices like controlling the body weight by regular exercise and healthy diet, avoiding smoking and alcohol consumption, and the most important one is to control the blood sugar levels (21). These life style modifications are very subjective and sometimes difficult to achieve. So, there should be some drug that can help the diabetic patients to achieve good sugar control and also reduce the risks of the comorbid conditions that results in diabetes.

SGLT2 inhibitors are reported to have extra-glycemic effects in type 2 diabetic patients. Besides glycemic control, treatment of type 2 diabetes with SGLT2 inhibitors provides varied benefits to the patients in terms of weight reduction, management of hypertension, and the most important benefit of SGLT2 inhibitors is that they act in an insulin independent manner there by reducing the risks of developing hyoglycemia (22). This insulin independent mechanism of action allows the SGLT2 inhibitors to be used in the patients already taking insulin therapy.

The objective of the present study was to see the degree of changes of body parameters with any degree change in HbA1c over 12 weeks with different classes of SGLT2 inhibitors. We found that HbA1c%, visceral fat, and waist circumference significantly reduced in the patients. This reduction of HbA1c% with SGLT2 has been reported previously in type 2 diabetes patients (23). In the present study we observed that change in visceral fat was influenced by age, gender, baseline BMI, baseline visceral fat, and change in skeletal muscle trunk and change in waist circumference was influenced by baseline total fat, baseline skeletal muscle trunk, and change in BMI. These changes were independent of the baseline as well as changes in HbA1c%.

Patients with T2DM are associated with progressive and generalized loss of skeletal muscle mass and function (24). In the present study we observed that there was a significant reduction in visceral fat and waist circumference in the patients after 12 weeks of SGLT2I use but there was no significant effect of SGLT2I on the Skeletal muscle trunk. These reductions in visceral fat, and waist circumference were independent of HbA1c reduction. So, consistent with other reported studies, SGLT2I along with decreasing HbA1c also reduces body fat thereby providing extra glycemic benefit to all groups of diabetic patients.

Although SGLT2 inhibitors provide extra-glycemic benefits in the type 2 diabetic patients but there remains some safety issues related with the usage of SGLT2 inhibitors. There are studies that reported the incidences of genital mycotic infections, urinary tract infections, risks of dehydration, risks of diabetic ketoacidosis in the type 2 diabetes mellitus patients on SGLT2 inhibitors (25-27). The increased risk of urinary tract infections in SGLT2I users is attributed to increased

glucose concentration in urine which may help the pathogens for their growth and proliferation (28). Hence risk benefit analysis should be conducted in a larger scale to evaluate the use of SGLT2I in type 2 diabetes mellitus treatment. Seven different types of SGLT2I are in use (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, ipragliflozin, luseogliflozin, and tofogliflozin) (29). The most commonly used SGLT2I are *dapagliflozin*, *empagliflozin*, and *canagliflozin.* In the present study, SGLT2I used by the patients were *dapagliflozin* (36.36%), *empagliflozin* (15.15%), and *canagliflozin* (48.48%). Three of these SGLT2I showed extra-glycemic effects. The changes observed in terms of glycemic and non glycemic parameters were not affected by the type of SGPT2I used. Reports from animal studies indicate that all SGLT2 inhibitors show comparable effects in management of blood sugar levels but *ipragliflozin* and *dapagliflozin* were more effective than *tofogliflozin*, *canagliflozin*, *empagliflozin*, and *luseogliflozin* in the management of diabetes related complications like obesity, dyslipidemia, inflammation, and nephropathy but these observations were without any statistical significance (30). In the present study also we found that the three SGLT2I used (*dapagliflozin*, *empagliflozin*, and *canagliflozin*) showed no statistical significance in the effects on the glycemic and non-glycemic parameters.

The major limitation of the study was the low sample size. In the present study 33 representative type 2 diabetes mellitus patients were enrolled for analysis. So, this study should be extended in larger cohort of patients with longer follow up periods. Another limitation of this study was, the machine used for visceral fat assessment was Omraon HBF 375 Karada Scan as MR spectroscopy for visceral fat assessment is not available in all over our clinic area and not even in the nearest metropolitan city. To summarize, in the present study the significantly changed parameters post treatment were visceral fat, waist circumference, and HbA1c. Changes in these non glycemic parameters were not influenced by baseline HbA1c or change in HbA1c levels. Change in HbA1c was influenced by baseline BMI, visceral fat, skeletal muscle trunk, HbA1c but was not influenced by changes in other parameters and duration of diabetes. *Dapagliflozin*, *empagliflozin*, and *canagliflozin* had similar effects on the glycemic as well as non glycemic parameters. The SGLT2I used in the study affected the no-glycemic parameters in an HbA1c independent manner.

CONCLUSION

Visceral fat and waist circumference were the non glycemic body parameters that changed significantly in the T2DM patients with SGLT2I but these changes were not correlated with baseline as well as change in HbA1c levels. So, from the findings of the present study it can be concluded that different SGLT2I affect the non glycemic parameters like visceral fat and waist circumference change in T2DM patients independent of changes in HbA1c. Also, the three classes of SGLT2I used in the study had similar effects on the changes in glycemic as well as non glycemic parameters.

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