EFFECTS ON METABOLIC PARAMETERS OF ADDITION OF SGLT-2 INHIBITORS ON PATIENTS WITH TYPE 2 DIABETES INADEQUATELY CONTROLLED WITH DPP-IV INHIBITORS AND METFORMIN

Sanjay Chatterjee[1], Anirban Majumder[2], Subir Ray[1], Kingshuk Bhattacharjee[3]
1. Apollo Gleneagles Hospital, Kolkata, India, 2. KPC Medical College, Kolkata, India, 3. Biocon Ltd., Bangalore, India

BACKGROUND AND AIMS

Practice guidelines are open regarding choice of therapy after metformin. Insulin(INS), sulphonylureas(SU) and thiazolidinediones(TZD) may cause hypoglycemia or weight gain. Dipeptidyl peptidase-IV (DPP-IV) inhibitors are unlikely to produce that. Sodium-glucose transporter-2 (SGLT-2) inhibitors are newer agents with the advantage of weight loss. We have used SGLT-2 inhibitors – canagliflozin or, dapagliflozin, or, empagliflozin on T2D patients inadequately controlled (HbA1c 7%) with DPP-IV inhibitors plus Metformin and analyzed the results on glycemic and other metabolic parameters. Since Indian data of such therapy is scanty, this study is relevant because of the number of patients studied, duration of study, study variables and effects of three SGLT-2 inhibitors analyzed separately.

METHODS

Data of 101 T2D patients inadequately controlled (HbA1c 7%) with DPP-IV inhibitors plus Metformin who were prescribed canagliflozin 100 mg or, dapagliflozin 5 or, 10 mg, or empagliflozin 10 mg or, 25 mg once daily with mean follow-up duration of 23 weeks were analyzed. Subjects receiving INS, SU and TZD were excluded from analysis. Changes in weight, blood pressure, glycaemia, lipids, renal and hepatic parameters were studied. Subgroup analyses were done to see effects of three SGLT-2 inhibitors.

RESULTS

Results showed that addition of SGLT-2 inhibitors produced favorable effects on all metabolic parameters studied (Table 1 to Table 3)

Table 1. Baseline Characteristic Features of the Overall Study Subjects, N=101

Parameter	Mean	Std. Dev.	Median
Age, Years	47.76	11.08	47.00
Height, m	1.62	0.10	1.64
Weight, kg	81.48	14.61	80.00
BMI, kg/m²	30.72	4.91	30.33
SBP, mmHg	131.21	14.95	130.00
DBP, mmHg	79.50	8.39	80.00
FPG, mg/dl	155.55	47.80	150.00
PPPG, mg/dl	220.33	78.16	196.50
HbA1c,%	8.17	1.74	7.70
ALT, U/L	41.19	19.21	42.00
AST, U/L	40.46	31.37	30.00
CHOLESTROL, mg/dl	140.47	37.55	135.00
TG, mg/dl	147.58	73.54	130.00
HDL, mg/dl	39.10	9.31	39.00
LDL, mg/dl	80.60	29.48	76.00
NON-HDL, mg/dl	89.99	48.08	90.50
Creatinine, mg/dl	0.90	0.21	0.90
Duration, Weeks	22.46	14.38	16.50
TG/HDL1	4.07	2.64	3.36
ACR	37.53	89.37	12.90
Met Dose, grams/day	1441.54	505.79	1000.00

Co-morbidities	No. of subjects	%
HTN	64	63.36
Micro-albuminuria	23	22.77
Nephropathy	2	1.98
CHD	13	12.87
Fatty Liver	12	11.88
Dyslipidemia	71	70.29
Overweight/Obesity	73	72.27
Statin Usage	64	63.36
Hypothyroidism	21	20.79

Table 2. Change in Parameters in the Study after treatment with DPP-IV Inhibitors+ SGLT-2 Inhibitors + Metformin, N=101

Study Parameters	Baseline Mean	SD	Median	Follow-up Mean	SD	Median	p
Weight, kg	81.55	14.33	80.30	78.88	14.66	76.00	<0.0001
BMI, kg/m2	30.85	4.84	30.33	27.73	9.19	29.13	0.0002
SBP, mmHg	130.85	15.01	130.00	124.44	17.59	127.00	0.0035
DBP, mmHg	79.43	8.54	80.00	77.21	8.65	79.50	0.029
FPG, mg/dl	154.25	48.11	147.00	123.15	26.40	122.00	<0.0001
PPPG, mg/dl	218.29	66.05	196.00	176.60	54.56	165.00	<0.0001
HbA1c,%	8.09	1.68	7.65	7.33	1.60	7.00	<0.0001
CHOLESTEROL, mg/dl	140.82	37.50	135.00	135.77	32.44	131.44	0.25
HDL, mg/dl	33.97	9.31	39.00	39.04	9.30	39.00	0.61
LDL, mg/dl	81.04	29.50	76.50	76.81	29.27	72.00	0.25
Non-HDL, mg/dl	89.82	48.76	90.50	80.31	84.42	86.00	0.042
Creatinine, mg/dl	0.90	0.21	0.90	0.89	0.24	0.90	0.72
TG, HDL, mg/dl	4.08	2.68	3.32	3.87	2.57	3.19	0.55

P<0.05 considered as statistically significant, p computed by paired t-test

Study Parameters	IQ Range	Median	Range	Lower Quartlite	Median	Range	p
ALT	26-54	43	10-89	23.5-44	28 .5	8.4-71	0.012
AST	23.1-45	30	17-130	26-45	37	16-130	0.75
TG	95-173	123.5	26-418	91-163	120	54-316	0.202
ACR	8.4-28.5	12.9	0.6-574	8-23	13	2.97-199	0.22

P<0.05 considered as statistically significant, p computed by Signed rank test

Table 3. Changes in Parameters after treatment with SGLT2 inhibitors

Parameter	Canagliflozin (n=30) Baseline Mean SD	At Follow up Mean ±SD	p value	Dapagliflozin (n=40) Baseline mean± SD	at Follow-up Mean ±SD	p value	Empagliflozin (n=31) baseline Mean± SD	At Follow up Mean ±SD	p Value
BMI (Kg/m²)	30.62 ±4.62	28.42 ±6.95		30.09 ±4.88	26.84 ±10.24	0.0081	31.62 ±5.33	28.03 ±9.57	0.049
SBP (mmHg)	131.83 ±13.89	124.34 ±14.32	0.37	128.64 ±16.82	123.64 ±22.33	0.255	133.23 ±13.23	125.06 ±12.83	0.0002
DBP (mmHg)	79.27 ±7.77	76.41 ±8.04	0.50	78.72 ±7.02	77.38 ±9.30	0.5297	80.55 ±10.52	77.52 ±8.28	0.049
FPG (mg/dl)	165.33 ±47.90	127.96 ±26.98	0.027	150.90 ±45.99	121.11 ±49.32	0.0003	151.84 ±50.80	123.19 ±21.27	0.0024
PPPG (mg/dl)	222.30 ±81.85	173.27 ±58.65	0.021	231.62 ±80.88	176.24 ±61.49	0.0017	203.88 ±70.46	186.47 ±46.94	0.3
ALT (U/L)	38.57 ±21.76	33.56 ±16.43	0.17	42.16 ±17.56	30.90 ±11.72	0.0123	40.60 ±20.04	33.13 ±17.23	0.4548
Cholestrol (mg/dl)	150.77 ±39.16	138.88 ±27.82	0.74	141.16 ±31.60	30.90 ±34.33	0.0123	40.60 ±40.70	33.13 ±33.55	0.4548
TG (mg/dl)	149.00 ±79.03	129.17 ±57.28		144.63 ±76.45	132.78 ±43.44	0.3244	148.77 ±68.55	143.88 ±64.98	0.2231
HDLc (mg/dl)	40.15 ±8.91	38.57 ±7.91	0.78	39.03 ±7.14	39.81 ±9.48	0.5444	38.41 ±11.83	38.81 ±10.22	0.3723
LDLc (mg/dl)	87.62 ±31.68	80.87 ±25.40	0.78	83.34 ±27.99	79.39 ±34.06	0.6436	72.54 ±27.26	70.60 ±25.26	0.6232
Non-HDLc (mg/dl)	99.17 ±49.98	84.34 ±47.77	0.57	84.08 ±49.20	78.71 ±51.71	0.4831	88.87 ±46.26	79.50 ±44.90	0.0781
Creatinine (mg/dl)	0.84 ±0.25	0.84 ±0.29	0.47	0.91 ±0.19	0.91 ±0.22	0.59	0.95 ±0.18	0.92 ±0.21	0.4215
Urine ACR (mg/g)	18.41 ±26.87	18.42 ±19.59	0.91	33.71 ±47.82	36.88 ±52.87	0.91	57.15 ±143.56	29.48 ±56.39	0.2387
Duration (weeks)		22.0 ±12.21			25.73 ±15.66			19.9 ±9.84	
% of Patients with HbA1c <7%		46.67			45.0			45.16	

Figure 1: Changes in HbA1c after treatment with SGLT2 inhibitors

Canagliflozin: 8.39±1.97 (baseline), 7.17±1.19 (follow up), (p=0.008)
Dapagliflozin: 8.11±1.60 (baseline), 7.33±1.71 (follow up), (p=0.0005)
Empagliflozin: 8.05±1.75 (baseline), 7.61±1.82 (follow up), (p=0.65)
Baseline Mean (+SD); At Follow up Mean (+SD)
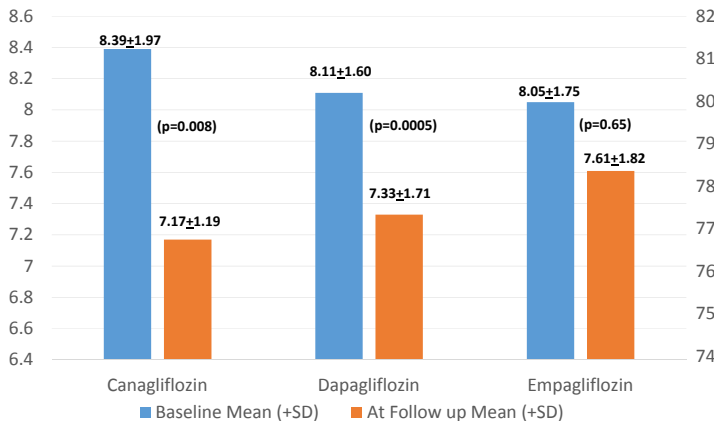
Figure 2: Changes in weight after treatment with SGLT2 inhibitors

Canagliflozin: 80.70±14.70 (baseline), 76.83±14.83 (follow up), (p=0.007)
Dapagliflozin: 81.27±15.25 (baseline), 80.01±15.80 (follow up), (p=0.002)
Empagliflozin: 81.46±13.14 (baseline), 78.16±13.43 (follow up), (p<0.0001)
Baseline Mean (+SD); At Follow up Mean (+SD)
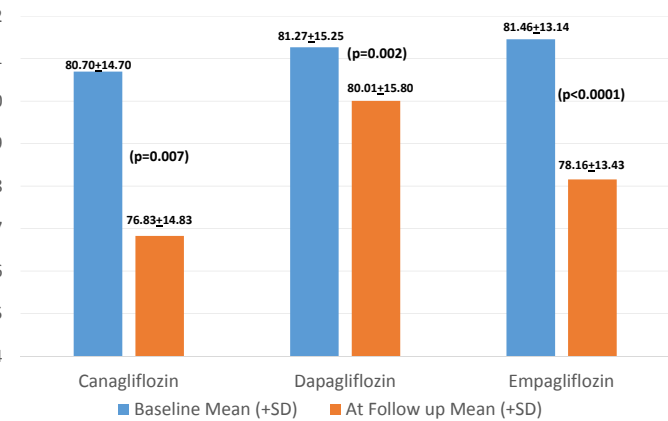
CONCLUSION

Our study shows that addition of SGLT-2 inhibitors on existing therapy with DPP-IV inhibitors and metformin produces favorable effects on metabolic parameters with the advantage of weight loss and without producing major hypoglycemic events.