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Letter to the Editor

Effect of Mizagliflozin on Postprandial Plasma Glucose in Patients With Functional Constipation

TO THE EDITOR: We read the recent review by Fukui et al[1] in this journal. In their paper, they referred that the bacterial product short chain fatty acid promotes glucose regulating hormones including glucagon-like peptide 1.[1] We consider their review to be accurate and to provide further insight to the following phenomena.

Mizagliflozin, a novel sodium-glucose cotransporter 1 inhibitor, suppresses the absorption of glucose and water in the intestine.[2,3] We reported that mizagliflozin showed favourable efficacy and safety for patients with functional constipation and the risk of hypoglycaemia would be low.[4] However, the dynamic data of postprandial plasma glucose under the administration of mizagliflozin has not been shown yet.

A randomised open-label study which evaluated the effects of oral administration of mizagliflozin 5 mg or 10 mg once daily at 30 minutes after breakfast for 2 weeks on plasma glucose and spontaneous bowel movement in patients with functional constipation was conducted in Japan (ClinicalTrials.gov NCT02343978). Twenty five patients (5 mg, n = 13 and 10 mg, n = 12) were enrolled in the study. After 2-weeks, postprandial plasma glucose and insulin at 1 hour and 2 hours in 10 mg of mizagliflozin and insulin at 2 hours in 5 mg of mizagliflozin were significantly lower than those in the baseline (Table). Areas under the curves for plasma glucose and insulin were not changed by 5 mg but significantly reduced by 10 mg of mizagliflozin (glucose, $P = 0.043$ and insulin, $P = 0.007$, one-sample t test). No hypoglycemic symptoms were induced by mizagliflozin but one patient showed hypoglycemic value (58 mg/dL) of postprandial plasma glucose at 2 hours in 10 mg of mizagliflozin. The mean number of spontaneous bowel movement per week significantly increased from 2.13 (SD, 0.45) at baseline to 7.99 (9.35) at week 2 in the 5 mg group and from 1.76 (0.62) to 6.81 (4.94) in the 10 mg group.

These results suggest that mizagliflozin actually inhibits postprandial glucose absorption from the intestine and has insulin-sparing effect. As Spiller[5] previously commented, altered microbiota by the luminal glucose is one of factors affecting the effect of mizagliflozin. Therefore, this study provides another evidence of the review by Fukui et al.[1] This study also supports the concept of low risk of hypoglycemia by sodium-glucose cotransporter 1 inhibitors[6], but low value of plasma glucose in rare cases should be recognized for further clinical studies.

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Table. Changes in Plasma Glucose and Insulin Levels in the Meal Tolerance Test in the 5 mg and 10 mg Group

Group	Weeks	Item	Times (hr)	n	Mean	SD	Min	Q1	Median	Q3	Max	*P*-value (week 0 vs 2)
Plasma glucose (mg/dL)												
Mizagliflozin 5 mg	0	FPG	0	13	94.2	11.1	79	87	92	100	114	-
		PPG	0.5	13	141.8	18.7	111	133	141	151	175	-
			1	13	139.2	41.9	88	104	131	165	219	-
			2	13	105.0	36.4	72	86	90	108	208	-
	2	FPG	0	13	95.1	13.0	77	87	91	101	124	0.665
		PPG	0.5	13	140.3	32.0	109	116	135	156	210	0.797
			1	13	125.8	48.2	81	98	110	129	231	0.216
			2	13	91.0	20.3	71	78	87	89	134	0.064
Mizagliflozin 10 mg	0	FPG	0	12	92.6	10.0	79	88	92	96	118	-
		PPG	0.5	12	143.4	31.0	107	121	141	150	206	-
			1	12	129.0	45.0	81	100	109	154	243	-
			2	12	105.8	28.5	76	84	100	124	163	-
	2	FPG	0	12	93.4	7.2	83	89	93	97	111	0.659
		PPG	0.5	12	144.6	20.4	105	127	147	159	177	0.839
			1	12	110.0	26.8	72	92	98	132	156	0.044
			2	12	82.6	14.6	58	76	83	91	105	0.009
Insulin (μU/mL)												
Mizagliflozin 5 mg	0	Fasting	0	13	5.28	2.24	2.7	3.8	4.9	5.6	10.1	-
		After meal	0.5	13	65.41	32.58	28.4	40.2	54.8	96.2	119.5	-
			1	13	58.07	25.60	18.8	40.8	49.5	70.9	105.8	-
			2	13	41.22	23.28	15.1	20.8	36.6	56.8	87.9	-
	2	Fasting	0	13	5.75	3.09	1.8	3.7	5.5	6.6	11.1	0·519
		After meal	0.5	13	68.16	31.28	22.7	46.6	63.9	89.0	121.3	0·504
			1	13	53.07	27.98	24.7	28.1	37.2	72.5	111.5	0·577
			2	13	13.62	8.16	4.5	7.0	10.6	19.6	32.6	< 0.001
Mizagliflozin 10 mg	0	Fasting	0	12	5.23	3.03	1.2	3.4	4.2	7.1	11.2	-
		After meal	0.5	12	79.03	74.08	21.8	37.5	58.1	93.6	296.0	-
			1	12	56.49	28.44	31.5	39.3	44.4	68.4	130.3	-
			2	12	35.34	12.58	18.1	23.3	36.5	45.5	57.7	-
	2	Fasting	0	12	4.89	1.77	3.2	3.9	4.5	5.2	9.9	0.634
		After meal	0.5	12	72.98	50.39	32.2	39.2	55.4	77.7	190.7	0.582
			1	12	39.88	17.11	18.8	21.6	39.9	55.1	64.9	0.021
			2	12	8.92	2.85	5.0	6.7	8.0	12.0	13.5	< 0.001

Min, minimum; Q, quartile; Max, maximum; FPG, fasting plasma glucose; PPG, postprandial plasma glucose.
At week 0 (without mizagliflozin) and 2 (with mizagliflozin), blood glucose and insulin levels were measured at 0, 30, 60, and 120 minutes after the patients ingested 431 kcal standard breakfast of 67.2 g to 68.5 g of carbohydrates, 5.4 g to 5.6 g of fat, and 19.7 g to 21.1 g of protein.
P-values were calculated using the one-sample *t* test.

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