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The SGLT2 inhbitor empagliflozin does not stimulate compensatory appetite responses in patients with excess adiposity and type 2 diabetes

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Abstract:
Background and aims: In patients with type 2 diabetes (T2D), SGLT2 inhibitors (SGLT2i) lower HbA1c and cause weight loss; however, observed weight change is less than predicted by modelling. This study tested the hypothesis that compensatory changes in appetite, and appetite-related hormones, explain this less-than-expected weight loss with SGLT2i.
Materials and methods: In a 24-week prospective, double-blind placebo-controlled trial, patients with overweight / obesity and T2D (age 30 - 75 years, BMI ≥ 25kg/m^2) were randomised (1:1:1:1) to one of four treatments: 1) placebo; 2) empagliflozin 25mg/day [EMPA]; 3) placebo and diet-induced weight loss [DIET]; 4) empagliflozin 25mg/day plus diet-induced weight loss [EMPA+DIET]; and assessed at 0, 2, 6, 12 and 24 weeks. DIET and EMPA+DIET groups reduced energy intake by 1500kJ/day. The primary outcome was circulating total peptide-YY (PYY) concentrations over a 3-hour mixed meal tolerance test (33% of daily energy requirements) at 24 weeks. Secondary outcomes included circulating concentrations of acyl ghrelin, GLP-1, leptin, appetite perceptions (100 mm VAS), body composition (DEXA) and physical activity (accelerometery). Data were analysed using generalised linear models at each time-point comparing each group with placebo; adjusting for baseline, age and BMI. Generalised estimating equations (GEE) examined overall treatment effects across follow-up.
Results: 68 participants were randomised (median [IQR]; age 63 [57, 69] years; BMI 31.8 [29.2, 35.1] kg/m^2; HbA1c 6.8 [6.6 -7.2]%; 35% female) with primary outcome data available for 61. Circulating concentrations of PYY were no different vs placebo in any treatment arm at 24 weeks (Table 1); but were elevated in EMPA at 12-weeks (P = 0.003). Circulating acyl ghrelin and GLP-1 were unchanged at all time-points; however, GEE showed that GLP-1 was higher in EMPA vs placebo (P = 0.016). Treatments had no effects on perceived huger or fullness. Lean mass was reduced in EMPA and EMPA+DIET vs placebo at 24 weeks ($P \leq 0.001$), with accordant (but not significant) reductions in resting metabolic rate. GEE highlighted a reduction in daily steps with EMPA vs placebo (P = 0.038); but not in the other treatment arms.
Conclusion: Empagliflozin does not provoke obvious compensatory appetite or appetite-related hormone responses in patients with excess adiposity and T2D. Additional studies should explore the effects of SGLT2i on hedonic drivers of eating behaviour.

Table 1 – treatment effects on primary and secondary outcomes at 24 weeks (vs placebo)

	DIET		EMPA		EMPA + DIET	
	Coefficient (95% CI)	*P*	Coefficient (95% CI)	*P*	Coefficient (95% CI)	*P*
PYY (pg/mL)*	-8.59 (-28.58, 11.40)	0.400	13.42 (-6.13, 32.97)	0.179	0.97 (-18.01, 19.95)	0.920
Acyl Ghrelin* (pg/mL)	3.19 (-17.69, 24.06)	0.765	-13.79 (-34.26,6.68)	0.187	-13.50 (-33.47, 6.47)	0.185
GLP-1 (pmol/L)*	1.21 (-4.14, 6.56)	0.657	3.08 (-2.17, 8.32)	0.250	0.34 (-4.77, 5.45)	0.896
Leptin (ng/mL)	-1.2 (-5.5, 3.1)	0.588	0.6 (-3.6, 4.9)	0.774	-4.8 (-8.9, 0.7)	0.022
Fat mass (kg)	-1.94 (-3.72, -0.16)	0.033	-0.98 (-2.71, 0.74)	0.264	-4.06 (-5.76, -2.36)	<0.001#
Lean mass (kg)	0.34 (-0.50, 1.18)	0.428	-1.41 (-2.23, -0.60)	0.001#	-1.60 (-2.40, -0.80)	<0.001#
RMR (kcal/d)	-59 (-249, 132)	0.545	-133 (-311, 45)	0.143	-176 (-352, 0)	0.050
Steps (per day)	604 (-698, 1906)	0.363	-800 (-2047, 447)	0.209	574 (-695, 1843)	0.375
Body mass (kg)	-1.52 (-3.79, 0.76)	0.191	-2.23 (-4.45, -0.01)	0.049	-5.62 (-7.79, -3.44)	<0.001#
HbA1c (%)	-0.09 (-0.47, 0.28)	0.626	-0.38 (0.74, -0.02)	0.041	-0.42 (-0.78, -0.06)	0.021

*Time averaged response during a 3 h mixed-meal tolerance test; #Significant after sequential Holm Bonferroni correction.

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