**Title**

The SGLT2 inhibitor 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 (SGLT2is) 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 SGLT2is.

**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/m2 ) were randomised (1:1:1:1) to one of four treatment arms: 1) placebo [PLA]; 2) empagliflozin 25mg/day [EMPA]; 3) 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 were supported to reduce 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 estimated daily energy requirements) at 24 weeks. Secondary outcomes included circulating concentrations of acyl ghrelin, GLP-1, leptin (fasted), subjective appetite perceptions (100 mm visual analogue scales), body composition (DEXA) and physical activity (waist-worn accelerometry). Data were analysed using generalised linear models at each time-point comparing each group with PLA; adjusting for baseline, age and BMI. Generalised estimating equations (GEE) examined overall treatment effects irrespective of time-point.

**Results:** 68 participants were randomised (median [IQR]; age 63 [57, 69] years; BMI 31.8 [29.2, 35.1] kg/m2; HbA1c 6.8 [6.6 -7.2]% 51 (49-55mmol/mol); diabetes duration 6 [4,10] years; 35% female; with primary outcome data available for 61. Circulating concentrations of PYY were no different vs PLA in any treatment arm at 24 weeks; but were elevated in EMPA at 12 weeks (*P* = 0.003). Circulating acyl ghrelin and GLP-1 remained unchanged at all time-points; however, GEE showed that GLP-1 was generally higher in EMPA vs PLA (*P* = 0.016). Body mass and HbA1c were reduced in EMPA; with greater effects seen in EMPA+DIET (Table 1). Study treatments had no effects on perceived hunger or fullness. Lean mass was reduced in EMPA and EMPA+DIET vs PLA at 24 weeks (*P* ≤ 0.001), with accordant nominal (but not significant) reductions in resting metabolic rate. GEE highlighted a reduction in daily steps with EMPA vs PLA (*P* = 0.038; non-sig after adjustment for multiple comparisons); but not in the other treatment arms.

**Conclusions:** Empagliflozin does not provoke obvious compensatory changes in appetite or appetite-related hormones in patients with excess adiposity and T2D; but was linked with lower physical activity levels. Additional studies are needed to scrutinise the effects of SGLT2is on reward-related (hedonic) drivers of eating behaviour.

**Table 1 – treatment effects on clinical and appetite-related hormones at 24 weeks (vs placebo)**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **DIET** | | **EMPA** | | **EMPA + DIET** | |
|  | Coefficient  (95% CI) | *P* | Coefficient  (95% CI) | *P* | Coefficient  (95% CI) | *P* |
| **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 |
| **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 |

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