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## A phase 1, single-blind, placebo-controlled, 3-arm cross-over trial assessing the appetite enhancing effects of potentially ghrelinergic dairy-derived peptides

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### Abstract

Methods to stimulate appetite in the sick or elderly remains a challenge with few safe therapeutic options. Ghrelin is an orexigenic hormone, increasing appetite and subsequent food intake. It has received considerable attention as a therapeutic target to stimulate food intake in patients with anorexia. The identification of food-grade bioactives with proven orexigenic effects would mark significant progress in the treatment of disease-related malnutrition. This study therefore investigated the effects of two milk-derived ghrelinergic peptides on appetite and energy intake in healthy humans.

A single-blind, placebo-controlled, 3-arm (placebo, casein bioactive MF1145 and whey bioactive UL-2-141) cross-over trial was conducted in healthy male volunteers. Participants received 26 mg/kg of both the bioactives and placebo. The main outcome measures were energy & protein intake from a set breakfast and *ad libitum* lunch and subjective appetite sensations as assessed by visual analogue scale (VAS). Basal and postprandial levels of active ghrelin (AG) were measured. Dietary intakes were analysed using Nutritics software. Statistical analyses were performed in R.

Overall, 22 male participants (mean age 27 years) were included, average BMI was 24.6 kg/m<sup>2</sup>, (19.8 to 30.2 kg/m<sup>2</sup>). Mean energy and protein intakes at lunch when treated with placebo were 1343 kcal (95% CI: 1215–1471 kcal) and 74 g (95% CI: 66–81 g), respectively. Energy and protein intakes were not significantly different from placebo for either treatment ( $p = 0.918$ ,  $p = 0.319$  for UL-2-141 and  $p = 0.889$ ,  $p = 0.959$  for MF1145, respectively). Similarly, appetite, hunger and satiety responses on VAS were not significantly different from placebo for either treatment. AG peak post-lunch on placebo was 653 pg/ml (95% CI: 511–794 pg/ml). Treatment with UL-2-141 resulted in 139 pg/ml reduction in post-prandial AG compared to placebo and treatment with MF1145 resulted in 114 pg/ml reduction compared to placebo. This pattern was significant for both treatments ( $p = 0.021$  and  $p = 0.045$ , respectively) however when controlling for fasting-AG, the pattern was no longer significant ( $p = 0.590$  and  $p = 0.877$  respectively). Pre-prandial AG peaks were not significantly different across treatments.

While these peptides have previously demonstrated ghrelinergic effects in rats, no effect on appetite or food intake in humans was identified by this study. This may be attributable to the small sample size or low dose. However, since healthy adults are often not in tune with their own physiological hunger, they may not respond strongly to simple physiological modulators and repeating the study in subjects with established anorexia may be prudent.

### Conflict of Interest

There is no conflict of interest