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Investigating the effect of sex and ketosis on weight-loss-induced changes in appetite

Anna Lyngstad,1,2 Siren Nymo,1,3 Silvia R Coutinho,1 Jens F Rehfeld,4 Helen Truby,5 Bård Kulseng,1,2 and Catia Martins1,2

1Obesity Research Group, Department of Clinical and Molecular Medicine, Faculty of Medicine and Health Science, Norwegian University of Science and Technology Trondheim, Norway; 2Centre for Obesity and Innovation (ObCe), Clinic of Surgery, St. Olav University Hospital, Trondheim, Norway; 3Nord-Trøndelag Hospital Trust, Clinic of Surgery, Namsos Hospital, Norway; 4Department of Clinical Biochemistry, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark; and 5Department of Nutrition, Dietetics & Food, Monash University, Melbourne, Australia

ABSTRACT

Background: Diet-induced weight loss (WL) is usually accompanied by increased appetite, a response that seems to be absent when ketogenic diets are used. It remains unknown if sex modulates the appetite suppressant effect of ketosis.

Objective: The aim of this study was to examine if sex modulates the impact of WL-induced changes in appetite and if ketosis alters these responses.

Methods: Ninety-five individuals (55 females) with obesity (BMI [kg/m²]: 37 ± 4) underwent 8 wk of a very-low-energy diet, followed by 4 wk of refeeding and weight stabilization. Body composition, plasma concentration of β-hydroxybutyrate (β-HB) and appetite-related hormones (active ghrelin, active glucagon-like peptide 1 [GLP-1], total peptide YY [PYY], cholecystokinin, and insulin), and subjective feelings of appetite were measured at baseline, week 9 in ketosis, and week 13 out of ketosis.

Results: The mean WL at week 9 was 17% for males and 15% for females, which was maintained at week 13. Weight, fat, and fat-free mass loss were greater in males (P < 0.001 for all) and the increase in β-HB at week 9 higher in females (1.174 ± 0.096 mmol/L, P = 0.029). Basal and postprandial GLP-1 and postprandial PYY (all P < 0.05) were significantly different for males and females. There were no significant sex × time interactions for any other appetite-related hormones or subjective feelings of appetite. At week 9, basal GLP-1 was decreased only in males (P < 0.001), whereas postprandial GLP-1 was increased only in females (P < 0.001). No significant changes in postprandial PYY were observed over time for either sex.

Conclusions: Ketosis appears to have a greater beneficial impact on GLP-1 in females. However, sex does not seem to modulate the changes in the secretion of other appetite-related hormones, or subjective feelings of appetite, seen with WL, regardless of the ketotic state. This trial was registered at clinicaltrials.gov as NCT01834859. Am J Clin Nutr 2019;109:1511–1518.

Keywords: ghrelin, glucagon-like peptide 1, peptide YY, cholecystokinin, hunger, fullness, prospective food consumption, ketosis, very-low-energy diet, weight loss

Introduction

Obesity has become a major public health problem worldwide (1). Fortunately, a sustained weight loss (WL) of 5–10% of initial weight is associated with several health benefits, including a reduction in many obesity-related risk factors and comorbidities (2). However, WL is usually followed by an increased drive to eat (3–5). Increased feelings of hunger are thought to be an important contributing factor to the high attrition rate seen in WL attempts and the difficulty in adhering continuously to a dietary energy restriction (6, 7). The compensatory increase in appetite observed during and after WL is thought to be partially driven by changes in the plasma concentration of appetite-related hormones, with an increase in the plasma concentration of the hunger-hormone ghrelin (3, 8), and a reduction in satiety peptides, such as glucagon-like-peptide-1 (GLP-1), peptide YY (PYY), and cholecystokinin (CCK) (3, 9–11).

Interestingly, a review by Gibson et al., in 2015, found that if WL is induced with ketogenic diets, either by a very-low energy diet (VLED) or by a ketogenic low-carbohydrate diet, the drive to eat is absent or reduced while subjects are ketotic (12). This is supported by other studies, which report...
no changes in subjective feelings of appetite (13–16), or the plasma concentrations of ghrelin with WL, while participants are ketogenic (13, 17–20). However, studies examining the impact of WL, under ketogenic conditions, on the plasma concentration of satiety peptides have mixed results. Three studies reported that plasma concentrations of satiety peptides were unchanged (11, 13, 19), whereas others reported a decrease in active GLP-1, total PYY, and CCK, in both the fasting and postprandial state (15, 17, 18, 21). The majority of the interventions described to date had small sample sizes (11, 13, 16), which may be underpowered to detect changes in all gut peptides. The majority of the studies included in the systematic review and meta-analysis by Gibson et al. were conducted in young females (12). Given that ketosis modulates appetite sensations (22) and the secretion of several appetite-related hormones (23), the question of whether males and females respond differently has not been explored. The aim of this analysis was to assess if sex modulates the changes in objective and subjective measures of appetite associated with WL, both in and out of ketosis.

**Study Design, Subjects, and Methods**

This paper reports a secondary analysis of the “Weight-loss maintenance and compensatory mechanisms activated with a VLED” study, approved by the Norwegian regional ethics committee (Ref., 2012/1901), registered in clinicaltrials.gov (NCT01834859), and conducted according to the guidelines laid down in the Declaration of Helsinki. All participants provided written informed consent before commencement. The primary outcome of the study was WL maintenance at 1 y, after an initial 8-wk VLED and these results are previously published (24). Secondary outcomes were changes in appetite and energy expenditure in response to the WL induced by the VLED (18, 25). To provide context for this secondary data analysis, subjects were healthy adults (18–65 y, 40 males and 55 females) with obesity (30 < BMI < 50 kg/m²) who were recruited via newspaper advertising serving the community of Trondheim, Norway. Entry criteria were that participants were weight-stable (<2 kg body weight change over the last 3 mo), not currently dieting to lose weight, and with an inactive lifestyle (<150 min of physical activity of at least moderate intensity per week) (26). Owing to the known effect of phase of menstrual cycle on appetite (27), females were postmenopausal, were taking hormonal contraceptives, or had a very regular menstrual cycle (28 ± 2 d). The study excluded pregnant or breastfeeding women and anyone with clinically significant illness, including diabetes, previous WL surgery, and/or taking medication known to affect appetite or induce WL. Participants were provided with an 8-wk ketogenic VLED, followed by 4 wk of refeeding, which was supervised and tailored to individual energy needs by a registered dietician.

**Weight-loss phase**

Participants followed a ketogenic VLED (Allevo, Karo Pharma AS, Sweden) for 8 wk, 550/660 kcal/d for females and males, respectively (42% carbohydrate, 36% protein, 18% fat, and 4% fiber). No-energy fluids were allowed ad libitum. Intake of low-starch vegetables (max 100 g/d) was encouraged, to provide dietary fiber.

**Weight-stabilization phase**

At week 9, participants were gradually reintroduced to regular food while reducing the intake of VLED products. An individual diet plan was tailored to individual energy requirements—resting metabolic rate × physical activity level (extracted from individual physical activity activity monitors [BodyMedia®, SenseWear] at week 8)—with 15–20% protein, 20–30% fat, and 50–60% carbohydrate, which was aimed at weight stabilization (28).

**Objective measures of compliance**

**Diet.**

Participants were provided with weekly individual 20-min consultations with a dietician, to review their food records. Urine acetooacetetatic acid concentration was measured weekly using Ketostix reagent strips (Bayer Corp.). Participants who were not ketotic were educated on how to improve their compliance with the prescribed dietary plan. Participants were considered not compliant and were excluded, if they were not ketotic for more than 1 consecutive week.

**Physical activity.**

Body Media (SenseWare) armband activity monitors were provided and worn for 7 d at baseline, weeks 8 and 12. Data were considered valid if participants wore the device for ≥4 d, including at least 1 weekend day, on more than 95% (22.8 h/d) of the time (29).

**Data collection**

The following measurements were performed in the fasting state at baseline, week 9 (the day immediately after the end of the VLED), and week 13.

**Body weight and composition.**

Air-displacement plethysmography (BodPod, COSMED) was used to record fat mass (FM) and fat-free mass (FFM).

\[ \beta\text{-Hydroxybutyric acid (}\beta\text{-HB)} \]

The plasma concentration of \( \beta\text{-HB} \) in the fasting state was measured with a Ketone Body Assay Kit (Mark134, Sigma-Aldrich).

**Appetite measures.**

Subjective appetite feelings (hunger, fullness, desire to eat, and prospective food consumption [PFC]) were measured using a validated 10-cm visual analog scale (30), and blood samples were collected in the fasted state and then every 30 min (0, 30, 60, 90, 120, and 150 min) after a standardized breakfast (600 kcal: 17% protein, 35% fat, and 48% carbohydrate) (31, 32), for a period...
of 2.5 h. Plasma samples were analyzed for active ghrelin (AG), total PYY, active GLP-1, and insulin using a Human Metabolic Hormone Magnetic Bead Panel (LINCOplex Kit, Millipore) and CCK using an “in-house” RIA method (33) (intra- and interassay CV were <10% and <20% for AG, GLP-1 and PYY; <10% and <15% for insulin, and <5% and <15% for CCK, respectively).

Power calculation
Sample-size estimation was based on expected differences in appetite suppression while under ketosis, between sexes. For an expected difference of 1 cm in the changes in fasting hunger feelings at week 9 (in ketosis) between sexes, assuming an SD of 1.6 cm, for a power of 80% and a statistical significance of 0.05, 84 participants would be needed. To allow for an expected drop-out rate of 15%, 97 participants were deemed necessary.

Statistical analysis
Statistical analysis was performed using SPSS version 24 (SPSS Inc.), and data presented as estimated marginal mean ± SEM, except for baseline characteristics where mean ± SD are given. Statistical significance was set at \( P < 0.05 \). Data were analyzed using linear mixed-effects models, with restricted maximum-likelihood estimation, including fixed effects for time and sex, and their interaction. The Benjamini–Hochberg method was used for main effects and post hoc pairwise comparisons, which controls for the false discovery rate, to adjust for the fact that we have examined a large number of variables (34). Results are reported for all completing participants if no significant sex \( \times \) time interaction was found and separately for males and females if a significant sex \( \times \) time interaction was present.

The total AUC for subjective feelings of appetite and appetite hormones was calculated from 0 to 150 min using the trapezoid rule. Correlations between \( \beta \)-HB plasma concentrations and changes in appetite were analyzed using the Spearman rank correlation test. All participants with available data on at least 2 out of the 3 time-points were considered completers and included in the analysis.

Results
One hundred subjects met the study entry criteria and started the study. Five males did not complete the 8-wk VLED (2 did not tolerate the VLED, 1 was excluded owing to consumption of extra food, 1 withdrew for personal reasons, and 1 was lost to follow-up), and 1 female did not complete measurements at week 13 (withdraw due to family illness). Ninety-five participants (55 females; 15 postmenopausal, 9 with a very regular menstrual cycle, and 21 taking hormonal contraceptives) were, therefore, included in this completer’s analysis with a mean age of 43 ± 10 y, and a BMI of 37 ± 4. Males were significantly younger (40 ± 9 compared with 44 ± 10 y, for males and females respectively, \( P < 0.01 \)) and had a higher body weight at baseline than females (119.8 ± 19 compared with 102.3 ± 12.8 kg, \( P < 0.001 \), respectively), but there were no differences in BMI.

Compliance
Diet.
Compliance with the VLED was excellent, and no participant was excluded based on negative acetoacetic acid concentration in the urine.

Physical activity.
No change in physical activity over time was recorded (data not shown).

Body weight and body composition
Changes in body weight and body composition are reported in Table 1. Eight weeks of following the VLED resulted in a 15.9% (17.9 ± 0.4 kg) WL, which was sustained at week 13 (18.4 ± 0.5 kg). A significant sex \( \times \) time interaction was observed for weight, FM, and FFM (\( P < 0.001 \) for all). Males had a greater weight (kg and %), FM, and FFM (kg) loss than females at week 9 (17% [20.6 ± 0.5 kg]) compared with 15% (15.3 ± 0.5 kg), \( P < 0.001 \) for both, for body weight, 15.5 ± 0.5 compared with 12.2 ± 0.4 kg, \( P < 0.001 \) for FM and 4.9 ± 0.3 compared with 3.1 ± 0.3 kg, \( P < 0.01 \) for FFM, respectively. These differences were also apparent at week 13, with males achieving a greater reduction in weight, FM, and FFM (from baseline) than females.

Ketosis
Changes in \( \beta \)-HB plasma concentration over time are reported in Table 1. \( \beta \)-HB increased significantly between baseline and week 9 (\( P < 0.001 \) for all) and decreased between week 9 and 13 (\( P < 0.001 \) for all), with concentration at week 13 no longer being different from baseline. A significant sex \( \times \) time interaction was present (\( P = 0.029 \)), with a smaller increase in \( \beta \)-HB plasma concentration, from baseline to week 9, in males than in females (0.783 ± 0.112 compared with 1.174 ± 0.096 mmol/L, respectively).

Appetite-related hormones
Changes in basal plasma concentration of appetite-related hormones are reported in Table 2. There were no significant sex \( \times \) time interactions for basal plasma concentration of appetite-related hormones, with the exception of active GLP-1 (\( P = 0.048 \)). No significant changes from baseline were seen for basal AG concentration at week 9, under ketosis, in all participants. Basal AG plasma concentrations increased significantly from week 9 to 13 (\( P < 0.001 \)) and were significantly higher than baseline at week 13 (\( P < 0.001 \)). A significant decrease in basal GLP-1 plasma concentration was clear at week 9 in males only (\( P < 0.001 \)). No changes over time occurred for basal total PYY plasma concentration. Basal plasma concentrations of CCK decreased significantly from baseline to week 9 (\( P < 0.001 \) and
and females (including fixed effects for time, sex, and their interaction. Symbols denote significant changes overtime:

| Basal | Baseline-week 9 | Baseline-week 13 | Week 9–week 13 | P value for sex \times time interaction |
|-------|-----------------|------------------|----------------|-----------------------------------------|
| Body weight, kg | | | | |
| Males | 119.8 ± 2.3 | −20.6 ± 0.5*** | −20.3 ± 0.6*** | 0.2 ± 0.6 | <0.001 |
| Females | 102.3 ± 1.9 | −15.3 ± 0.5** | −16.5 ± 0.8** | −1.1 ± 08 | |
| Fat mass, kg | | | | |
| Males | 47.0 ± 1.6 | −15.5 ± 0.5*** | −18.0 ± 0.6*** | −2.5 ± 0.6*** | <0.001 |
| Females | 49.2 ± 1.4 | −12.2 ± 0.4*** | −14.4 ± 0.8*** | −2.2 ± 0.8** | |
| Fat-free mass, kg | | | | |
| Males | 71.6 ± 1.0 | −4.9 ± 0.3*** | −3.2 ± 0.3 | 1.7 ± 0.3*** | <0.001 |
| Females | 53.0 ± 0.9 | −3.1 ± 0.3*** | −1.8 ± 0.4 | 1.3 ± 0.4** | |

1Values are estimated marginal means ± SEMs. Data were analyzed using linear mixed-effects models with restricted maximum-likelihood estimation, including fixed effects for time, sex, and their interaction. Symbols denote significant changes overtime: ***P < 0.001, **P < 0.01. Males had a significantly larger weight, fat mass, and fat-free mass loss (P < 0.001 for all) and a smaller increase in β-hydroxybutyric acid at week 9 (P = 0.029) than females.

TABLE 2 Baseline and changes in basal plasma concentrations and AUC of appetite-related hormones over time in all participants (n = 95), males (n = 40) and females (n = 55)

| Basal | Baseline-week 9 | Baseline-week 13 | Week 9–week 13 | P value for sex \times time interaction |
|-------|-----------------|------------------|----------------|-----------------------------------------|
| Active ghrelin, pg/mL | | | | |
| All | 96.9 ± 8.1 | 3.6 ± 6.9 | 43.4 ± 9.0*** | 39.8 ± 9.0*** | 0.211 |
| Active glucagon-like peptide 1, pg/mL | | | | |
| Males | 9.4 ± 2.8 | −5.0 ± 1.2*** | −1.7 ± 1.3 | 3.3 ± 1.3 | 0.048 |
| Females | 6.4 ± 2.4 | −0.8 ± 1.1 | −2.0 ± 2.0 | −1.2 ± 2.0 | |
| Total peptide YY, pg/mL | | | | |
| All | 47.0 ± 6.0 | −12.1 ± 5.1 | 0.7 ± 6.6 | 12.8 ± 6.6 | 0.497 |
| Cholecystokinin, pmol/L | | | | |
| All | 1.02 ± 0.06 | −0.26 ± 0.07*** | 0.07 ± 0.09 | 0.33 ± 0.09*** | 0.593 |
| Insulin, pg/mL | | | | |
| All | 1098 ± 53 | −715 ± 57*** | −604 ± 74*** | 111 ± 74 | 0.162 |
| Postprandial, AUC | | | | |
| Active ghrelin, pg/mL-min | | | | |
| All | 10.383 ± 835 | 662 ± 599 | 4559 ± 777*** | −3897 ± 777*** | 0.141 |
| Active glucagon-like peptide 1, pg/mL-min | | | | |
| Males | 2010 ± 365 | −171 ± 180 | −349 ± 194 | −179 ± 194 | 0.015 |
| Females | 1939 ± 322 | 573 ± 162*** | −316 ± 290 | −889 ± 290** | |
| Total peptide YY, pg/mL-min | | | | |
| Males | 9803 ± 1354 | −1317 ± 1040 | −1232 ± 1151 | 85 ± 1151 | 0.016 |
| Females | 7683 ± 1233 | 3077 ± 970 | −798 ± 1577 | −3875 ± 1579 | |
| Cholecystokinin, pmol/L-min | | | | |
| All | 388 ± 15 | −100 ± 12*** | −26 ± 15 | 74 ± 15*** | 0.723 |
| Insulin, pg/mL-min | | | | |
| All | 626,864 ± 31,193 | −265,956 ± 28,440*** | −287,575 ± 36,879*** | −21,619 ± 36,903 | 0.262 |

1Values are estimated marginal means ± SEMs. Data were analyzed using linear mixed-effects models with restricted maximum-likelihood estimation, including fixed effects for time, sex, and their interaction. Symbols denote significant changes overtime: ***P < 0.001, **P < 0.01. Only males experienced a significant reduction in basal active glucagon-like peptide 1 from baseline to week 9. Only females experienced an increase in active glucagon-like peptide 1 AUC from baseline to week 9. AUC, area under the curve.
postprandial plasma concentration of appetite–related hormones, with the exception of active GLP-1 (P = 0.015) and PYY (P = 0.016). No significant change in the AUC for AG was recorded between baseline and week 9, but by week 13 when refeeding occurred, there was a significant increase from baseline and from week 9 (P < 0.001 for both). A significant increase in active GLP-1 AUC was seen in females only at week 9 (P < 0.001), followed by a significant fall between weeks 9 and 13 (P < 0.0001). No significant changes were found for active GLP-1 AUC at week 13, compared with baseline, in either males or females. Despite a significant sex × time interaction for total PYY AUC, no significant sex differences over time were apparent.

A significant reduction in CCK AUC was clearly seen while participants were ketotic at week 9 (P < 0.001), and an increase from week 9 to week 13 (P < 0.001), with CCK AUC at week 13 being no longer different from baseline. A significant reduction in insulin AUC was observed with WL at both weeks 9 and 13, compared with baseline (P < 0.001 for both).

### Subjective feelings of appetite

Changes in subjective appetite feelings in the fasting state are listed in Table 3. No significant sex × time interaction was apparent for subjective feelings of appetite in the fasting state. A significant increase in hunger was clear at week 9, when participants were ketotic (P < 0.05), followed by a further rise with refeeding (P < 0.05). No significant changes overtime were found for fullness. A significant increase was seen in feelings of desire to eat at week 13 (P < 0.05), but not at week 9, compared with baseline. A significant decrease in feelings of fullness was reported at week 9 (P < 0.001), but not at week 13, compared with baseline.

Postprandial ratings of appetite over time are listed in Table 3. Supplemental Figure 2 displays the AUC observations graphically. No significant sex × time interaction was recorded for postprandial ratings of appetite. Hunger AUC decreased from baseline to week 9 (P < 0.01), followed by an increase with refeeding (week 13: P < 0.05). No significant differences were seen in hunger AUC between baseline and week 13. Participants rated their feelings of fullness as increased from baseline to week 9 (AUC, fullness P < 0.001), which was followed by a decrease with refeeding, by week 13 (P < 0.01). These subjective feelings of fullness returned to baseline levels, with no significant change in AUC fullness between baseline and week 13.

Participants rated their desire to eat similarly, with a significant reduction in desire to eat at week 9 (P < 0.05) and returning to baseline levels by week 13. The AUC for PFC also decreased significantly at week 9 (P < 0.01) feelings in the fasting state. There were no significant correlations between either β-HB plasma concentration or WL (kg/%) and other appetite markers.

### Correlation analysis

A higher β-HB concentration at week 9 was associated with a greater increase in active GLP-1 AUC (from baseline to week 9) in females only (ρ = 0.4, P < 0.01). A greater WL at week 13 was associated with a greater increase in hunger (ρ = 0.6, P < 0.05) and desire to eat (ρ = 0.71, P < 0.01) feelings in the fasted state. There were no significant correlations between either β-HB plasma concentration or WL (kg/%) and other appetite markers.

### Discussion

The aim of this analysis was to investigate if sex modulates the changes in appetite seen with WL, both in and out of ketosis. This

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### TABLE 3 Baseline and changes in subjective feelings of appetite during fasting and AUC over time in all participants (n = 95)

|                   | Baseline | Δ Baseline–week 9 | Δ Baseline–week 13 | Δ Week 9–week 13 | P value for sex × time interaction |
|-------------------|----------|-------------------|--------------------|----------------|-----------------------------------|
| **Fasting**       |          |                   |                    |                |                                   |
| Hunger, cm        | 3.8 ± 0.2| 0.6 ± 0.3*        | 1.5 ± 0.4***       | 0.9 ± 0.4*     | 0.43                              |
| Fullness, cm      | 2.3 ± 0.2| 0.5 ± 0.2         | 0.4 ± 0.3          | −0.2 ± 0.3     | 0.581                             |
| Desire to eat, cm | 4.5 ± 0.2| 0.01 ± 0.2        | 0.8 ± 0.3*         | 0.8 ± 0.3*     | 0.928                             |
| Prospective food consumption, cm | 5.9 ± 0.2 | −1.1 ± 0.3*** | −0.3 ± 0.3         | 0.8 ± 0.3*     | 0.468                             |
| **Postprandial (AUC)** |          |                   |                    |                |                                   |
| Hunger, cm-min    | 342.0 ± 23.7| −49.8 ± 22.0**   | 22.0 ± 28.6        | 71.8 ± 28.6*   | 0.309                             |
| Fullness, cm-min  | 876.1 ± 26.0| 209.8 ± 30.4***  | 84.3 ± 38.8        | −125.6 ± 38.9**| 0.134                             |
| Desire to eat, cm-min | 415.0 ± 27.6  | −66.7 ± 23.9*    | −16.2 ± 31.1       | 50.5 ± 31.1    | 0.184                             |
| Prospective food consumption, cm-min | 659.5 ± 32.8 | −184.9 ± 32.3** | −162.4 ± 41.7*** | 22.5 ± 41.7    | 0.843                             |

1Values are estimated marginal means ± SEMs. Data were analyzed using linear mixed-effects models with restricted maximum-likelihood estimation, including fixed effects for time, sex, and their interaction. Symbols denote significant changes overtime: ***P < 0.001, **P < 0.01, *P < 0.05. The changes in subjective appetite feelings over time were not statistically significant different between sexes, AUC, area under the curve.
was achieved by secondary analysis of a longitudinal weight-loss study where healthy adult participants undertook a VLED diet for 8 wk to induce ketosis and then transitioned to a food-based weight maintenance diet and reversal of the ketotic state between week 9 and week 13 (19). With the exception of changes in basal and postprandial GLP-1, which were more favorable in females while in ketosis, the changes in both plasma concentration of appetite-related hormones and subjective feelings of appetite seen with WL, both in and out of ketosis, were similar for both males and females.

Basal and postprandial AG plasma concentrations were unaltered while participants were ketogenic, despite a 16% WL. These finding corroborate with previous evidence showing that WL induced by ketogenic diets has no impact on active (17–20) or total ghrelin (13). Furthermore, an increase in AG was WL induced by ketogenic diets has no impact on active (17–20) or total ghrelin (13).

Our study did not reveal any significant changes in total PYY (3) have been reported after WL in mixed samples. Some research suggests that subjective feelings of appetite may explain the divergent results.

When out of ketosis (week 13), an increase in hunger was observed in the fasting state, which concurs with the majority of the literature (17, 18, 20, 42). After a meal, feelings of PFC were reduced. It remains uncertain if 4 wk of refeeding and weight stabilization is sufficient for energy balance to be re-established in subjects with obesity.

Interestingly, our findings show little correlation between β-HB plasma concentration and changes in hunger or AG during ketosis. The only correlation observed was for a higher ketosis to be associated with a larger GLP-1 AUC in females. Even though the appetite suppressant effects of ketogenic diets is well established (12), the exact mechanisms mediating specifically the absence (or lower) increase in hunger and ghrelin while in ketosis remain to be fully elucidated (43).

The present analysis has several strengths. First, the sample size is much larger than in previous studies and has a more balanced sex distribution. Second, both objective and subjective appetite markers during fasting plus in response to a meal were assessed. Third, compliance with the diet was excellent, and participants remained weight-stable after refeeding, with objective measures of compliance by using both urinary and blood ketone levels at all time-points. This analysis also has some limitations. A multiplex kit was used to measure AG, active GLP-1, total PYY, and insulin, which is likely to result in less accurate and precise measurements than optimized assays for each individual hormone. Moreover, the energy load of the standardized meal was not adjusted for body size, so that the larger active GLP-1 secretion reported in the postprandial state in females only could potentially be due to the fact that the test meal represented a larger proportion of energy needs in females compared with males. As the mean age difference was 4 y, we have not adjusted for age in our analysis, and even though some research suggests that subjective feelings of appetite may change with aging (22), this difference was unlikely to have any substantial impact. Finally, the intake of low-starch vegetables during the ketotic phase of the diet was not quantified or taken into account in the analysis, as we relied on objective measures of ketosis as a measure of diet compliance.

Ketogenic VLEDs induce WL effectively in adults, both males and females, and should, therefore, be considered as a potential
Ketosis can minimize the expected increase in hunger apparent in adults regardless of the ketotic state. Increased subjective feelings of hunger and satiety. Increased subjective feelings of hunger with beneficial impact on GLP-1 secretion in females, sex alone does not appear to modulate the secretion of gut peptides that signal hunger and satiety. Increased subjective feelings of hunger with the drive to eat should be expected after refeeding. Participant-centered strategies need to be in place to reduce the risk of overeating and relapse in the long-term to help prevent weight regain.

In conclusion, even though ketosis seems to have a more beneficial impact on GLP-1 secretion in females, sex alone does not appear to modulate the secretion of gut peptides that signal hunger and satiety. Increased subjective feelings of hunger with the drive to eat should be expected after refeeding. Participant-centered strategies need to be in place to reduce the risk of overeating and relapse in the long-term to help prevent weight regain.

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The authors’ responsibilities were as follows—CM, HT, and BK: designed the research; SN and AL: conducted the research, analyzed the data, and wrote the paper; JFR: performed the analysis of CCK; CM: had primary responsibility for the final content; and all authors: read and approved the final manuscript. None of the authors report a conflict of interest related to research presented in this article.

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