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A walnut-containing meal had similar effects on early satiety, CCK, and PYY, but attenuated the postprandial GLP-1 and insulin response compared to a nut-free control meal

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Abstract

Regular nut consumption is associated with lower adiposity and reduced weight gain in adulthood. Walnut feeding studies have observed minimal effect on body weight despite potential additional energy intake. Several mechanisms may explain why consuming nuts promotes weight control, including increased early phase satiety, possibly reflected in postprandial response of gastrointestinal and pancreatic peptides hypothesized to affect appetite. The purpose of this study was to compare postprandial insulin, glucagon and gastrointestinal peptide response and satiety following a meal with ~54% of energy from walnuts or cream cheese, using a within-subject crossover study design in overweight/obese adults (N = 28). Sixty minutes after the walnut-containing meal, glucagon-like peptide-1 was lower than after the reference meal (p=0.0433), and peptide YY, cholecystokinin and ghrelin did not differ after the two meals. Sixty and 120 min after the walnut-containing meal, pancreatic polypeptide (p = 0.0014 and p = 0.0002) and glucose-dependent insulinotropic peptide (p < 0.0001 and p = 0.0079) were lower than after the reference meal, and 120 min after the walnut-containing meal, glucagon was higher (p=0.0069). Insulin and C-peptide increased at 60 min in response to both meals but were lower at 120 min after the walnut-containing meal (p=0.0349 and 0.0237, respectively). Satiety measures were similar after both meals. These findings fail to support the hypothesis that acute postprandial gastrointestinal peptide response to a walnut-containing meal contributes to increased satiety. However, inclusion of walnuts attenuated the postprandial insulin response, which may contribute to the more favorable lipid profile observed in association with regular walnut consumption.

Keywords

Walnuts; Insulin; Postprandial gastrointestinal peptides; Satiety

1. Introduction

Although energy intake compared to expenditure is the ultimate determinate of weight loss or weight gain, dietary strategies are sorely needed to facilitate a sustained reduction in

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energy intake that promotes weight management and/or weight reduction for overweight and obese individuals. Gastrointestinal peptides hypothesized to affect appetite potentially contribute to the control of food intake by affecting appetite and early phase satiety, and they exhibit differential responses to various dietary strategies such as modified diet composition and food form (Delzenne et al., 2010; Sobrino Crespo, Perianes Cachero, Puebla Jimenez, Barrios, & Arilla Ferreiro, 2014). Exploring these responses to foods and dietary factors may provide insight and help to identify useful dietary strategies to promote long-term weight management.

Regular consumption of nuts has been negatively associated with adiposity in several large cohorts (Mattes & Dreher, 2010; Mattes, Kris-Etherton, & Foster, 2008; Natoli & McCoy, 2007). For example, women in the Nurses' Health Study who reported eating nuts ≥2 times/ week had less weight gain and lower risk of obesity than did women who rarely ate nuts when followed prospectively (Bes-Rastrollo et al., 2009). In an analysis that combined three separate cohorts of men and women who were followed for nearly 20 years, intake of nuts was one lifestyle and dietary factor found to be inversely associated with weight gain in adulthood (Mozaffarian, Hao, Rimm, Willett, & Hu, 2011). The PREDIMED trial examined the effect of three dietary interventions on risk for cardiovascular disease outcomes, one of which involved supplementation of the diet with nuts, and changes in body weight did not differ across diet groups but participants assigned to supplemental nut consumption showed a significant decrease in central obesity (Babio et al., 2014).

The specific effects of consuming various nuts in a weight loss intervention have been examined in a few studies and have had mixed results (Abazarfard, Salehi, & Keshavarzi, 2014, pp. 457–64; Foster et al., 2012; Li et al., 2010; Pelkman et al., 2004; Wien, Sabate, Ikle, Cole, & Kandeel, 2003). In a recent randomized clinical trial, we observed that prescribing walnuts, despite their high energy density, was associated with weight loss comparable to a standard lower fat diet, and better than a higher fat, lower carbohydrate diet without walnuts, in the context of reduced energy intake and a behavioral weight loss program (Rock et al., 2016).

Several mechanisms have been suggested to explain why consuming energy-dense nuts is generally not associated with weight gain and may facilitate weight management (Mattes et al., 2008; Natoli & McCoy, 2007). Nuts may promote satiety, which could modulate appetite and promote dietary compensation; e.g., total energy intake may be spontaneously reduced due to greater satiety and satiation association with nut consumption. Also, recent evidence using modern methods has revealed that walnuts contribute less metabolizable energy in humans than is calculated by proximate analysis and standardized Atwater estimates (Baer, Gebauer, & Novotny, 2016). Further, walnuts are rich in polyunsaturated fatty acids (PUFA), which are associated with higher postprandial thermogenesis compared to meals high in saturated fat (Casas-Agustench et al., 2009) and may also influence the satiety response (Kozimor, Chang, & Cooper, 2013). Satiety is potentially reflected in the postprandial response of the gastrointestinal peptides hypothesized to be involved in the control of satiety and appetite (Delzenne et al., 2010). Feelings of satiety, fullness, and hunger following walnut consumption has been examined in only two previous studies (Brennan, Sweeney, Liu, & Mantzoros, 2010; Casas-Agustench et al., 2009), and the postprandial gastrointestinal

peptides response following walnut consumption has been examined in only one of these studies (Brennan et al., 2010).

The purpose of this study was to compare postprandial insulin, glucagon and gastrointestinal peptide response and satiety following a meal with or without walnuts, using a within-subject crossover study design in overweight/obese adults (N = 28). We also examined self-reported satiety following these meals using a visual analog scale.

2. Methods

2.1. Subjects

Subjects were non-diabetic overweight and obese men and women (N = 28) who met the following inclusion criteria: Aged 21 years and older, body mass index (BMI) ≥27.0 kg/m^2 and ≤40 kg/m^2; non-smoker; willing and able to participate in clinic visits and telephone and Internet communications; willing to allow blood collections; and with no known allergy to tree nuts. Prior to enrollment, subjects were screened for diabetes and considered ineligible with a fasting blood glucose ≥125 mg/dL. The UCSD institutional review board approved the study protocol, and all participants provided written informed consent.

2.2. Study design and protocol

This study was a within-subject crossover study design. Demographic data were collected and height and weight of participants were measured during screening, and BMI was calculated as kg/m^2. All subjects completed two meal feeding clinic visits one week apart, at which the subject consumed, in randomized order, either a breakfast meal containing walnuts or a meal without walnuts (the reference meal). Participants were instructed to eat their regular dinner prior to the day of the meal feeding clinic visit and fast for at least 12 h prior to their visit time. They were asked to eat a similar dinner meal for both days prior to the clinic-based test meals. Liquids consumed with the meal (e.g., water, tea, coffee) were monitored to ensure equivalent intake during the two meals. Participants were instructed to consume the test meal within 20 min and were monitored and observed to adhere to this protocol.

The energy content of the test meal was individualized to contain approximately 30% of total energy requirements estimated using the Harris Benedict equation (Frankenfield, Muth, & Rowe, 1998) and ranged from 400 to 600 kilocalories. Table 1 shows the nutrient content of the 500 kcal meal, and amounts of the food items were adjusted accordingly to meet the other energy levels. Macronutrient distribution of the test meal was matched at each energy level. Fiber content was similar although slightly higher in the walnut-containing meal compared to the reference meal (i.e., 8.8 g versus 6.0 g in the 500 kcal meal). Although total fat content was similar in the two meals, saturated fat was higher in the reference meal because walnuts contain substantial amounts of PUFA (47% of the fat grams) and monounsaturated fatty acids (MUFA, 9% of the fat grams). All test meals were prepared by the same investigative team on the morning of each of the study days.

At each of the two meal feeding clinic visits, fasting blood specimens were collected from each subject before the meal, and additional blood specimens were provided at 30, 60, and

120 min after the meal. BD-P800 tubes (BD, Franklin Lakes, NJ, USA) containing protease, esterase, and DPP-IV inhibitors were used for collecting the blood used in the analysis of gut hormones. After blood collection and separation, plasma aliquots were stored at −80° C in cryogenic tubes until analysis.

3. Measurements

3.1. Laboratory measures

The MILLIPLEX MAP Human Gut Hormone Panel (EMD Millipore, Merck KGaA, Darmstadt, Germany) was used for the simultaneous quantification of the following analytes: glucagon-like peptide-1 (GLP-1) (active), ghrelin (active), pancreatic polypeptide (PP), glucose-dependent insulinotropic peptide (GIP), peptide YY (PYY) (total), C-peptide, insulin, and glucagon. Cholesystokinin (CCK) was measured using the ELISA RayBio Human CCK EIA kit (Ray Biotech, Norcross, GA, USA).

3.2. Visual analog scale (VAS)

Concurrent with each of the four blood draws at each meal visit, subjects were asked to rate their satiety by answering three questions on a visual analog scale (VAS). Each of the questions was presented to the participant on a computer screen within a REDCap (Research Electronic Data Capture, Vanderbilt University, Nashville, TN, USA) database, with a 100 mm horizontal line anchored at either end, so that answers could be indicated on a continuous scale. This general approach has been shown to have validity, reliability, and reproducibility (Gibbons, Finlayson, Dalton, Caudwell, & Blundell, 2014). The questions were: “How hungry do you feel?” with anchor values ranging from “I am not hungry at all” (scored as 0) to “I have never been more hungry” (scored as 100); “How full do you feel?”, with anchor values ranging from “Not at all full” (scored as 0) to “Totally full” (scored as 100), and “How much do you think you could eat now?” with anchor values ranging from “Nothing at all” (scored as 0) to “A lot” (scored as 100). We also constructed a satiety index using the mean of the three satiety questions, where hunger and “how much could you eat” were scored inversely (100 – VAS value).

3.3. Power calculation and statistical analysis

Our analysis plan noted that a sample size of 20 subjects in a crossover design was adequate to distinguish between changes in both PYY and GIP after a walnut-containing meal compared to a placebo test meal (Brennan et al., 2010). This sample size did not provide power to distinguish differential responses for insulin, active ghrelin, or GLP-1.

Statistical analysis was conducted using a repeated measures mixed model for each analyte, assuming unstructured covariance. Main effects in each model were time (before eating time 0, and 30, 60, and 120 min after eating) and meal type (reference being the cream cheese-containing reference meal and the experimental meal containing walnuts). The interaction between meal and time was also included as a predictor of outcome in each model. Each multivariate model tested the hypothesis that the responses did not vary by diet over time, and we present the global F statistic and significance for each analyte. In addition, we tested

the significance of the meal × time interaction at each distinct time point using an analysis of least squares mean difference within each mixed model.

As an exploratory analysis, baseline peptide levels were compared by sex and BMI to explore whether there were any differences based on those characteristics. The analysis for sex used independent t tests, and the analysis for BMI used linear regression analysis. In order to better understand the benefit of tailoring meals to the participant's energy requirements, we did an additional exploratory analysis in which we split our sample of 28 subjects into 14 subjects with a BMI <33 kg/m^2, and 14 subjects with BMI >33 kg/m^2, and tested for a difference in effect size of two selected analytes (insulin and C-peptide) at 60 and 120 min after eating.

We employed a Bonferroni correction for the 9 peptides and set alpha for type 1 error at 0.0056. All analysis was done with SAS version 9.4 (SAS Institute, Cary, NC, USA).

4. Results

Study participant characteristics are presented in Table 2. Self-reported satiety measures (feelings of hunger, fullness and anticipated prospective consumption) obtained with the VAS were similar in response to the two meals. The calculated satiety index also did not differ between the two meals at the baseline and follow-up time points (Fig. 1 and Table 3).

Prior to the meals, gut peptide levels did not differ by meal assignment. Men had higher insulin and C-peptide levels than women at baseline: insulin mean [SEM] 19 [1.6] μU/mL for men and 13 [1.1] μU/mL for women, $p = 0.0048$; C-peptide mean [SEM] 1898 (144) pg/mL versus 1493 (82) pg/mL ($p = 0.0116$). Men had lower levels of ghrelin than women (20 [4] pg/mL versus 48 [6]) pg/mL, $p = 0.0033$). Glucagon also was higher in men than women (52 [5] pg/mL versus 35 [6] pg/mL, $p = 0.0468$). The other analytes did not differ by sex. The only two analytes which were found to be associated with BMI, both directly, were insulin ($p = 0.0353$), and C-peptide ($p = 0.0016$). Based on analysis using a median split of BMI, BMI does not appear to modify effect size for either analyte at 60 and 120 min after eating.

Measured levels of ghrelin (active), CCK, GLP-1 (active), and PYY (total) are shown in Fig. 2 and Table 3. The only meal-related difference was observed at 60 min, where GLP-1 was lower after the walnut-containing meal. Postprandial PYY, ghrelin, and CCK did not differ between the meals at any of the time points (Fig. 2 and Table 3).

At 120 min after the walnut-containing meal, glucagon was higher than the reference meal, $p = 0.0069$ (Fig. 3 and Table 3). Insulin and C-peptide levels increased at 60 min in response to both meals but were lower at 120 min after the walnut-containing meal (p = 0.0349 and $p = 0.0237$ respectively). Additional postprandial peptide responses are shown in Table 4. At 30 min after the meal, the walnut-containing meal resulted in marginally lower levels of PP compared with the reference meal ($p = 0.0499$). At both 60 and 120 min after eating the walnut-containing meal, subjects had significantly lower levels of PP ($p = 0.0014$ and $p = 0.0002$) and GIP ($p < 0.0001$ and $p = 0.0079$) than they did after eating the reference meal.

Among the global models for each analyte, the models for GIP, C-peptide, and glucagon met the Bonferroni threshold for significance ($p < 0.0056$). Notably, the Bonferroni correction assumes independence of the analytes. Given the intercorrelation of some of our measures (e.g., GLP-1 and glucagon rho = 0.64, C-peptide and insulin rho = 0.85, C-peptide and GIP, rho = 0.57), the Bonferroni correction is likely to be unduly stringent.

5. Discussion

Results from this study suggest that acute effects of walnut consumption on postprandial gastrointestinal peptides do not explain the favorable effect of consuming nuts on weight management, at least in the phase of early satiety. These peptides have been hypothesized to contribute to satiety and the control of appetite and may be potential biomarkers, but assessing and interpreting these levels is complicated by the effects of variations in timing of their response and other influencing factors, such as habituation to meal patterns, food form, and degree of adiposity (Delzenne et al., 2010). Further, their relationship with satiety is not yet clear, with the lack of a correlation that has been observed between these peptides and self-reported satiety and satiation in many studies (Delzenne et al., 2010; Steinert et al., 2017). As recently reviewed by (Steinert et al., 2017), it remains unclear whether these gastrointestinal peptides have a physiological endocrine function that contributes to the control of eating.

We did observe an effect of walnut consumption on postprandial insulin, C-peptide and glucagon response, despite the similar energy and macronutrient contents of the meals. In many feeding studies, walnuts have been shown to lower low-density lipoprotein cholesterol and triglyceride levels (Kris-Etherton, 2014). Higher fasting and postprandial insulin levels, as occurs in association with insulin resistance, promotes increased fatty acid synthesis, elevated fasting triglyceride levels, and decreased high-density lipoprotein cholesterol (HDL-C) levels (Klop, Elte, Cabezas, 2013; Reaven, 2012). We found the beneficial effects of a walnut-rich diet on lipids, especially HDL-C and triglycerides, were especially pronounced for insulin resistant women (Le et al., 2016). Results from this study may be compared to two previous studies in which satiety following a walnut-containing meal was compared to that following a reference meal without walnuts. The acute effects of three high-fat meals on energy expenditure, substrate oxidation and satiety were compared in the study by Casas-Agustench et al. (2009), using a crossover trial design and VAS measure similar to the present study. Healthy men (N = 29) consumed three isocaloric meals: high in PUFA from walnuts (approximately 47 g walnuts), MUFA, or saturated fatty acids (SFA). The meal high in PUFA from walnuts was associated with similar satiety measures at 30, 90, 210 and 300 min postprandially, as compared to a meal high in MUFA from olive oil or a meal high in SFA from dairy products, which is in agreement with the findings of the present study.

In another study involving a sample of men and women with the metabolic syndrome (N = 63), a similar crossover design was used to examine the effect of a walnut-containing meal (48 g walnuts) or placebo, provided in a blenderized liquid formulation, on satiety and postprandial gut hormones and insulin measured daily over a four-day period (Brennan et al., 2010). On the first and last day of each visit, subjects had a fasting blood draw and

repeated blood samples collected every 30 min for 3 h following consumption of the liquid meal. Fullness, satiety, and hunger were assessed by a VAS before breakfast and lunch on each day of both visits. An increased sense of satiety and fullness were found on days 3 and 4 following the walnut-containing meal. Similar to the results of the present study, few differences in the postprandial peptide responses were observed. However, GIP levels were lower on days 1 and 4 following the walnut-containing meal than the reference meal as seen in the present study. Postprandial insulin was similar in response to the two meals in that study, unlike our observation, but the sample populations differed considerably in the two studies (theirs consisted entirely of individuals with metabolic syndrome, with higher levels of fasting insulin and insulin resistance).

This study has several strengths. One strength is the comparability of the two meals with regard to nutrient content, other than that due to the inclusion of walnuts in the test meal, which resulted in a substantial difference in the proportion of PUFA in that meal. In a previous study, PYY and satiety response (assessed via VAS similar to the present study) was compared over a 5-h period in a crossover design to PUFA-rich, MUFA-rich, and SFA-rich meals (Kozimor et al., 2013). The PUFA source in the meal in that study was sunflower oil and flaxseed oil, rather than walnuts, as in the present study. They found that the postprandial PYY response was lower for the MUFA-rich meal versus the SFA-rich or PUFA-rich meals, and the SFA-rich meal promoted greater subjective feels of fullness compared to the MUFA-rich or PUFA-rich meals.

A limitation of this study is that the postprandial blood samples were collected at specific intervals, and as previously noted, the timing and trajectory of the gut peptide response can vary considerably, so that maximal response may be missed without continuous measures. Even follow-up measures more frequent or over a longer time span than in the present study are at high risk of not capturing peak responses, affecting accurate interpretation of the response (Delzenne et al., 2010). Another limitation of this study is that the focus was on short-term, acute responses and early phase satiety, and measuring responses over the long-term would better model the observational studies relating nut consumption to adiposity and weight management. We assessed response to individual meals rather than assessing satiety over days or weeks of food intake. Notably, the degree of control and standardization that are ideal, as well as considerations of subject burden, make the application of this type of design and comparison difficult over long periods of time. Also, there are very few previous studies of the effect of nut consumption on gastrointestinal peptide response, which constrain estimating adequate sample size to achieve statistical power to detect differences.

In conclusion, these findings fail to support the hypothesis that acute postprandial gastrointestinal peptide response to a walnut-containing meal contribute to increased satiety after walnut consumption. However, the inclusion of walnuts in the meal attenuated the postprandial insulin response, which may contribute to the more favorable lipid profile that has been observed in association with regular walnut consumption.

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Abbreviations

BMI	body mass index
CCK	cholecystokinin
GIP	glucose-dependent insulinotropic peptide
GLP-1	glucagon-like peptide-1
HDL-C	high-density lipoprotein cholesterol
MUFA	monounsaturated fatty acid
PP	pancreatic polypeptide
PYY	peptide YY
PUFA	polyunsaturated fatty acid
SFA	saturated fatty acid
VAS	visual analog scale

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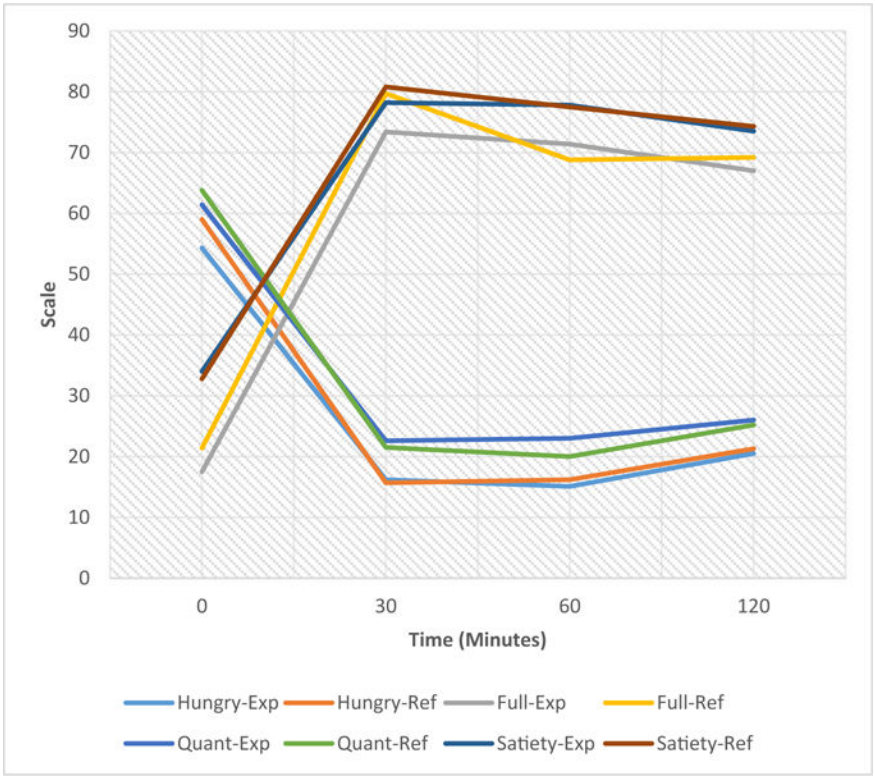

Fig. 1.

Satiety measures after experimental (walnut) or reference (control) breakfast. Questions were “How hungry do you feel” (“Hungry”), “How full do you feel” (“Full”), “How much do you think you could eat” (“Quant”). Satiety index (“Satiety”) is aggregated among the three questions on a 100-point scale. “Exp” denotes experimental meal, and “Ref” denotes reference meal.

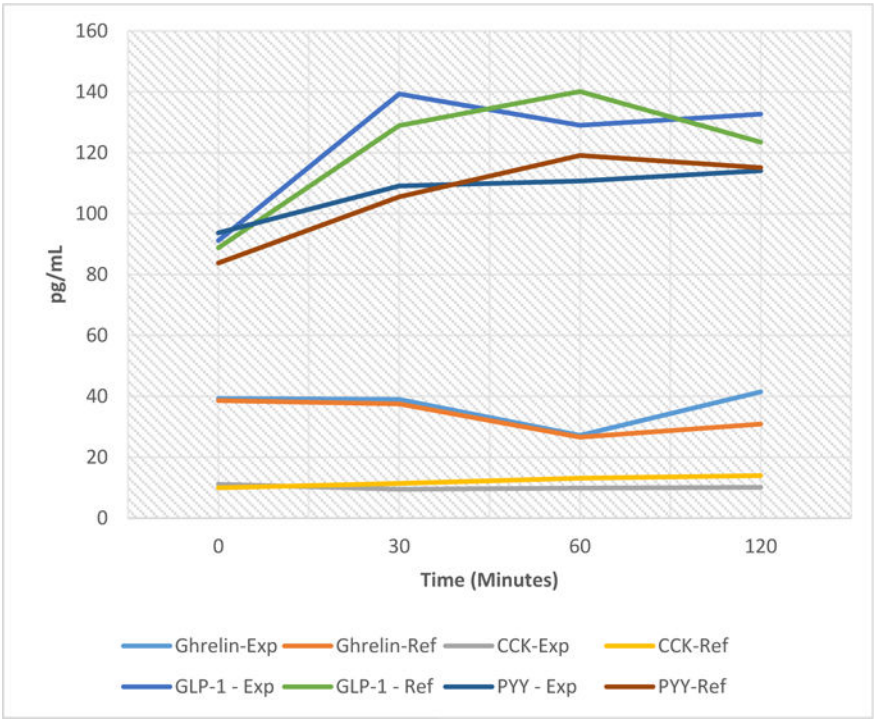

Fig. 2.

Ghrelin, cholecystokinin (CCK), glucagon-like peptide-1 (GLP-1), and peptide YY after experimental (walnut) or reference (control) breakfast. “Exp” denotes experimental meal, and “Ref” denotes reference meal.

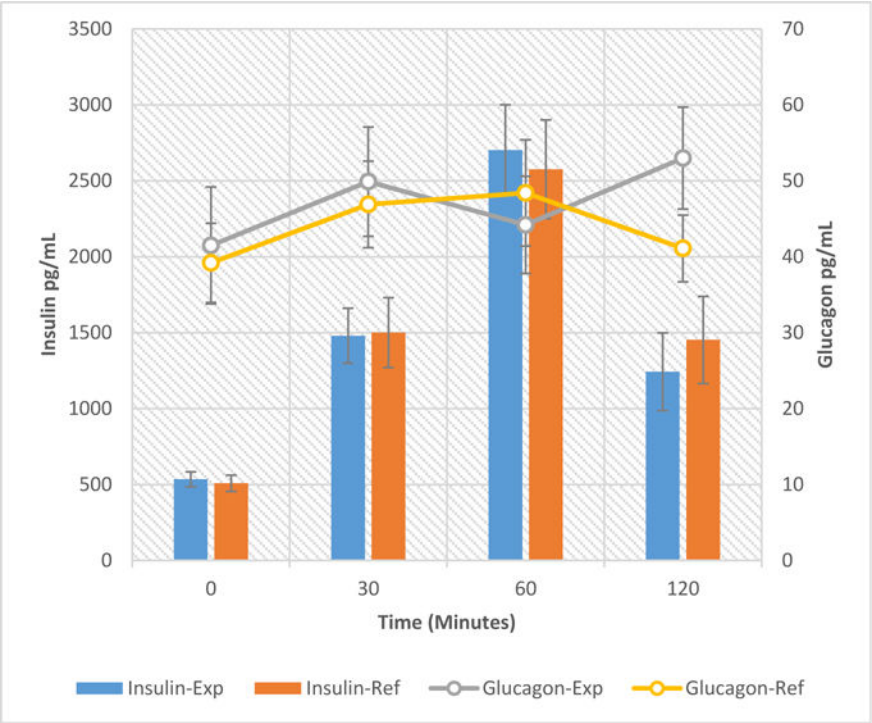

Fig. 3.

Insulin (bars) and glucagon (lines) after experimental (walnut) or reference (control) breakfast. “Exp” denotes experimental meal, and “Ref” denotes reference meal. Values shown are means and standard errors. Glucagon response was different by meal type, $p = 0.0031$.

Table 1

Nutrient content of the 500 kcal level meal.

Experimental Meal (walnut-containing):							
	Weight (g)	**Energy (kcal)**	**Protein (g)**	**Carbohydrate (g)**	**Fat (g)**	**SFA(g)**	**Fiber (g)**
Whole wheat bread[a]	78.0	180	9.0	40.5	2.3	0.0	4.5
Sugar free jam[b]	31.8	30	0.0	9.0	0.0	0.0	0.0
Strawberries[c]	76.0	25	0.5	6.0	0.0	0.0	1.5
Walnut pieces[d]	42.5	278	6.5	5.9	27.8	2.6	2.8
Total	228.3	513	16.0	61.4	30.0	2.6	
% of energy			12.5	47.9	52.7		
Reference Meal (no walnuts):							
	Weight (g)	**Energy (kcal)**	**Protein (g)**	**Carbohydrate (g)**	**Fat (g)**	**SFA(g)**	**Fiber (g)**
Whole wheat bread[a]	78.0	180	9.0	40.5	2.3	0.0	4.5
Sugar free jam[b]	31.8	30	0.0	9.0	0.0	0.0	0.0
Strawberries[c]	76.0	25	0.5	6.0	0.0	0.0	1.5
Cream cheese[e]	84.0	270	3.0	6.0	24.0	15.0	0.0
Total	269.8	505	12.5	61.5	26.3	15.0	6.0
% of energy			9.1	48.7	46.8		

SFA = saturated fatty acid.

[a]Nature's Harvest Stone Ground 100% Whole Wheat Bread, Bimbo Bakeries, PA, USA.

[b]Smuckers Sugar Free Jam, The J.M. Smucker Company, Orrville, OH, USA.

[c]Organic Strawberries, Driscoll Strawberry Associates, Inc. Watsonville, CA, USA.

[d]Walnuts, Diamond Foods, Inc. Stockton, CA, USA.

[e]Raskas Cream Cheese, Schreiber Foods, Inc. Green Bay, WI, USA.

Table 2

Subject characteristics (total N = 28; n = 19 female, n = 9 male).

	Mean (SD)	Range
Age (yrs)	49.1 (11.1)	39–67
Height (m)	1.66 (0.11)	1.47–1.84
Weight (kg)	91.8 (15.2)	69.7–132.3
BMI (kg/m^2)	32.9 (2.8)	27.6–39.4

Table 3

Model details for meal by time interaction for analytes in Figs. 1–3.

Analyte	Mean Difference	Standard Error of Mean Difference	*F*	Degrees of Freedom	P for Global Model
Hunger	−1.7	3.2	0.55	27	0.6508
Fullness	−2.2	3.9	1.32	27	0.2885
Quantity	0.4	3.1	0.71	27	0.5573
Average Satiety	−0.3	2.2	1.06	27	0.3833
GLP-1	8.4	5.7	4.83	27	0.0081
Ghrelin	3.4	3.8	2.19	27	0.1122
Cholecystokinin	2.5	1.9	1.98	27	0.1409
Glucagon	5.4	3.3	5.90	27	0.0031
Insulin	96	122	3.74	27	0.0228
Peptide YY	5.7	5.2	4.28	27	0.0135

Table 4

Additional postprandial peptide concentrations.

Analyte	Time (minutes)	Reference Meal, Mean (SD)	Walnut-Containing Meal, Mean (SD)	*p*-value	*F*	Degrees of Freedom	P for Global Model
PP, pg/mL	0	77 (58)	61 (48)	0.1077	3.31	27	0.0349
	30	318 (168)	266 (170)	0.0499			
	60	329 (162)	245 (135)	0.0014			
	120	307 (146)	249 (126)	0.0002			
GIP, pg/mL	0	76 (60)	68 (35)	0.3805	7.72	27	0.0007
	30	334 (330)	240 (128)	0.1255			
	60	656 (392)	388 (172)	<0.0001			
	120	515 (260)	392 (184)	0.0079			
C-peptide, pg/mL	0	1583 (536)	1663 (609)	0.3385	5.34	27	0.0051
	30	2700 (1212)	2781 (996)	0.6253			
	60	4238 (1597)	4310 (1537)	0.6983			
	120	3247 (1386)	2921 (1381)	0.0237			

SD = standard deviation.

PP = pancreatic polypeptide.

GIP = glucose-dependent insulinotropic peptide.