European Journal of Clinical Nutrition
https://doi.org/10.1038/s41430-017-0016-7

ARTICLE

Effects of lipid emulsion particle size on satiety and energy intake: a randomised cross-over trial

Sally D. Poppitt[1,2,3] · Stephanie C. Budgett[4] · Alastair K. MacGibbon[5] · Siew-Young Quek[6] · Sophie Kindleysides[1] · Katy R. Wiessing[1,2]

Received: 28 April 2017 / Revised: 26 August 2017 / Accepted: 10 September 2017

Abstract

Background/objectives Emulsified lipids, with central lipid core surrounded by polar lipid 'protective coat', have been proposed to stimulate the ileal brake, alter appetite, food intake and aid weight control. In addition to lipid composition, emulsion particle size may contribute to efficacy with small droplets providing a larger surface area for gastrointestinal (GI) lipase action and larger droplets prolonging and delaying digestion in the GI tract. Tube feeding studies delivering emulsions directly into the small intestine show clear effects of smaller particle size on appetite and food intake, but evidence from oral feeding studies is sparse. The objective of this study was to determine the effects of lipid emulsion particle size on appetite response and food intake.

Subjects/methods In a three-arm randomised cross-over, high-phospholipid (PL) dairy lipid emulsions or matched control were consumed at breakfast within a yoghurt smoothie: (i) large-particle size emulsion, LPE (diameter 0.759 μm, 10 g lipid emulsion, 190 g yoghurt), (ii) small-particle size emulsion, SPE (diameter 0.290 μm, 10 g lipid emulsion, 190 g yoghurt), (iii) control non-emulsion, NE (10 g non-emulsion lipid, 190 g yoghurt). Twenty male participants completed the study, where postprandial appetite response was rated using visual analogue scales (VAS) and *ad libitum* energy intake at a lunch meal measured 3 h later.

Results There was a trend for LPE to suppress hunger ($P = 0.08$) and enhance fullness ($P = 0.24$) relative to both SPE and NE but not statistically significant, and no significant effect of either emulsion on food intake at the lunch meal ($P > 0.05$).

Conclusions Altering particle size of a high-PL emulsion did not enhance satiety or alter eating behaviour in a group of lean men.

Introduction

Manipulating physical properties and structure of foods may offer the potential for regulation of appetite and body weight by controlling the release of macronutrients during the digestive process [1]. Lipid emulsions have been proposed to suppress energy intake, with arrival of these emulsions or their degradation products into more distal regions of the small intestine triggering the duodenal or ileal brake and subsequent appetite suppression [2–5]. While particle size (PS) is likely to be an important physical feature of the emulsion, evidence comes predominantly from enteral tube feeding studies [6, 7] and is yet to be convincingly demonstrated when lipids are consumed in dietary form. Hence we wanted to investigate the effects of altering lipid emulsion PS in a dietary study assessing appetite response and food intake.

✉ Sally D. Poppitt
s.poppitt@auckland.ac.nz

1 Human Nutrition Unit, University of Auckland, Auckland, New Zealand

2 School of Biological Sciences, University of Auckland, Auckland, New Zealand

3 Department of Medicine, University of Auckland, Auckland, New Zealand

4 Department of Statistics, University of Auckland, Auckland, New Zealand

5 Fonterra Research and Development Centre, Palmerston North, New Zealand

6 Department of Food Science, University of Auckland, Auckland, New Zealand

Published online: 24 November 2017

Both the duodenal and ileal brake are based on the principal that increased exposure of fat or other nutrients within the small intestine may stimulate a proximal feedback loop to in turn slow gastric emptying, slow small bowel motility, increase secretion of gut peptides and alter appetite response and food intake. Again, there is clear evidence of appetite suppression from enteral studies [7–12], and it is one of several effects proposed to underpin suppression of food intake following bariatric surgery, e.g., Roux-en-Y gastric bypass, where increased amounts of undigested contents of the jejunum are suggested to promote an intestinal brake [13, 14]. Evidence for a brake induced by dietary lipid arriving into the ileum was proposed from early studies of the commercial small PS (0.080 μm) emulsion Fabuless™. Originally shown to suppress food intake over hours and days [15–17] and with evidence of increased orocecal transit time [18], there remains poor consensus on its efficacy despite growing numbers of studies [19–25]. Two recent dietary studies have however reignited interest in the potential for oral emulsions to suppress appetite [26, 27]. First, a very small PS emulsion (0.100 μm), predominantly comprising high polar lipid oat oil, was reported to significantly increase circulating satiety-related gut peptides and also decrease energy intake (EI) when compared with large PS milk fat globules (1.00 μm) [26]. Second, a small PS lipid emulsion (0.400 μm), comprising predominantly sunflower oil plus locust bean gum stabiliser, was reported to suppress short-term food intake relative to large particles (6.00 μm) in a carefully conducted study, which included magnetic resonance imaging (MRI) to assess a range of gastrointestinal outcomes [27]. Clearly, lipid droplets of varying sizes may be metabolised differently due to lipase activity during lipid digestion [28], a consequence of differences in surface area available for enzyme activity [29] among other proposed mechanisms. In light of this recent evidence, we wanted to compare the effects of small and larger PS high-PL dairy emulsions. In order to do this, we assessed postprandial appetite-related sensations in addition to EI at a subsequent meal in two lipid:water emulsions and a non-emulsified lipid:water control given within a yoghurt-based breakfast smoothie.

Materials and methods

Participants

Participants who were lean (body mass index, BMI, 18–25 kg/m^2), 18–55-year-old males, and healthy as assessed through self-reported records were enroled into this study. Recruitment was conducted in Auckland, New Zealand via local newspapers and online methods. Participants were invited to the University of Auckland Human Nutrition Unit for an early morning screening visit at the appetite research centre (ARC). Exclusion criteria were overweight or obesity (current and prior), participation in a weight loss programme, medically diagnosed eating disorder, cigarette smoking within the previous 6 months, or any significant endocrine, metabolic or gastrointestinal disease. Participants were not enroled in the study if taking any medications associated with the regulation of appetite or body weight. Ethical approval was obtained from the Northern Region X, Health and Disabilities Ethics Committee (HDEC), Auckland, New Zealand. Informed consent was obtained in writing from each of the eligible study volunteers. Trial registration was completed prior to recruitment of participants, through the Australia and New Zealand Clinical Trial Registry: ACTRN12611000308998.

Study design

The two lipid emulsions and the non-emulsified lipid control were consumed at breakfast. Postprandial appetite response was then assessed throughout the morning, and *ad libitum* food intake measured at the subsequent lunch meal. All participants attended the ARC for study visits on three separate days, with randomisation assigned prior to the start of the trial. Between study visits, there was a minimum 3-day washout period where participants resumed their regular diet and pattern of physical activity. Prior to each study day, participants were asked to avoid alcoholic beverages, keep to their habitual diet pattern and not participate in strenuous exercise for 24 h. To promote compliance on the pretreatment days, participants recorded their food and beverage intake as well as time spent sitting, on-screen activities, standing, and undertaking activities estimated as mild/moderate/strenuous intensity.

Study procedures

The protocol for the study was based on the approach outlined by Blundell et al. [30], and also previous studies investigating food intake and eating behaviour at the Human Nutrition Unit ARC [23, 31–33]. At each study visit, the volunteers were asked not to exercise that morning and to arrive fasted over the previous 12 h (except water). The study visit commenced with measurement of fasted body weight (Seca, Model 708, Germany), and 125 ml of water given to drink. Any adverse events (AEs) between study visits were reviewed and recorded. Height was measured only at the screening visit (Seca, model 222, Germany). Prior to breakfast, fasting baseline visual analogue scales (VAS) were completed to rate subjective hunger and fullness, as well as satisfaction and current thoughts of food (TOF)/prospective consumption [30]. Breakfast was between 0900-0915 h with participants consuming the

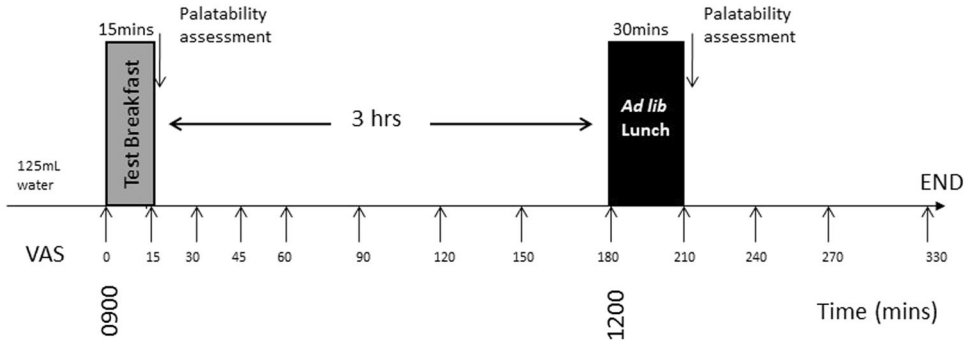

Fig. 1 Daily protocol

yoghurt smoothie within a maximum of 15 min. VAS ratings were measured throughout the morning, and participants remained within the ARC throughout the postprandial assessment and had a sedentary morning. The lunch meal was served 3 h later at 1200 h, within individual dining booths, with participants screened from each other and with no external distractions throughout the 30-min period. No mobile phones, laptops or other screen activities were permitted during the meal. VAS ratings continued to be measured for 2 h after the lunch. Participants were asked to remain within the ARC throughout each study day, where they had a low activity day but were not permitted to sleep. The daily study protocol for each of three identical study days is shown in Fig. 1.

Lipid treatments

The three lipid treatments comprised of two dairy lipid plus water emulsions of varying lipid droplet size and one lipid plus water control, which was not emulsified. A high-phospholipid (PL) emulsifier, dairy phospholipid concentrate 700 (PC700; Fonterra Co-operative Group, New Zealand), was included in all treatments both emulsions and non-emulsion. The three breakfast treatments were (i) dairy lipid emulsion with high-PL emulsifier, small-PS emulsion (SPE); (ii) dairy lipid emulsion with high-PL emulsifier, large PS emulsion (LPE); (iii) dairy lipid non-emulsified control (NE). Identical lipids were used in each treatment, with variation in PS achieved through a different ratio of core lipid:PL:water, and different processing conditions. The fatty acid (FA) profile for all treatments was that of a typical dairy lipid (C16:0 27%; C18:0 11%; other saturated FA 26%; C18:1 29%; other unsaturated FA 7%). All treatments were given at the breakfast meal as part of a dairy yoghurt smoothie, based on findings from a previous study conducted in our laboratory, which observed greater VAS fullness associated with yoghurt plus lipid emulsion, as opposed to lipid emulsion served alone or with other solid food formats [23]. Lipid emulsions and control were combined with the semi-liquid yoghurt just prior to serving the breakfast, and hence there was no processing step.

The emulsions were developed and prepared at the Department of Food Science, University of Auckland. SPE and NE both comprised 7.2 g core dairy lipid plus 1.8 g PC700 plus 21 g water, and LPE comprised 8.28 g core dairy lipid plus 0.72 g PC700 plus 21 g water. Ten grams of SPE, LPE and NE were added to the yoghurt on each occasion (Table 1). To prepare the test products, both the lipid and water were warmed in a microwave, combined by pipette and then pre-homogenised (APV 2000, SPX FLOW Inc, NC, USA; setting 3) for 3 min. After 20 min at RT, the pre-homogenisation was then repeated for 1 min. Each sample was then put into a microfluidizer (M-110L Microfluidizer Processor, MFIC Corporation, MA, USA) at 12,000 psi, and repeated as required (SPE for three cycles; LPE five cycles). The non-emulsion sample (NE) was prepared by combining core lipid, PL and water components and mixed by gentle stirring, with no homogenisation step. Following each preparation, treatments were stored overnight refrigerated at 4 °C and then given to the participants as per the randomisation schedule the next morning.

A Zetasizer (Nano ZS series, Malvern, UK) was used to assess PS, with dynamic light scattering or photon correlation spectroscopy. The rate of intensity fluctuation was used to calculate diameter of emulsified high-PL lipid droplets. Viscosity and refractive index were measured using a rheometer (RVDV–III+, Brookfield Engineering, Middleboro, MA, USA). Mean (SD) PS was SPE: 0.290 (0.012) μm and LPE: 0.759 (0.025) μm. Lipid characteristics were assessed in pilot trials, where identical conditions to that of the intervention trial were replicated, including the overnight cool storage. The energy content plus the composition of the macronutrients for the three breakfasts was calculated using dietary software based on New Zealand food composition (FoodWorks Professional, V5, 1998 to 2007; Xyris, Brisbane, Australia, Table 2).

VAS

Participants were required to rate their hunger and fullness, satisfaction and TOF throughout each study day using VAS ratings, as previously described [23, 24, 30, 31, 33]. The

Table 1 Energy and macronutrient composition of the three test breakfasts

	Emulsion lipid/water (g)	PS Z-average (d·nm)	PDI	Yoghurt (g)	Weight (g)	Energy (kJ)	ED (kJ/g)	Fat (%en)	CHO (%en)	Protein (%en)
SPE[a], small particle size emulsion$_{\text{dairy lipid + PC700}}$	10	290 ± 11.8	0.4 ± 0.03	190	200	790	4	27	55	14
LPE[b], large particle size emulsion$_{\text{dairy lipid + PC700}}$	10	759 ± 24.8	0.4 ± 0.02	190	200	790	4	27	55	14
NE, non-emulsified$_{\text{dairy lipid + PC700}}$	10	—	—	190	200	790	4	27	55	14

Each of the test lipids was stirred into a semi-liquid dairy yoghurt and given as a 200 g smoothie (5.7 g fat, 27.4 g CHO, 6.5 g protein) at breakfast

Emulsions prepared by mixing, pre-homogenisation, plus 3[a] or 5[b] repeat microfluidiser cycles at 12,000 psi. An emulsifying agent was added to all test lipid products, including the non-emulsion. Particle size of lipid:water (ratio 30:70) emulsions measured in triplicate by Zetasizer using dynamic light scattering (DLS), where Z-average particle diameter (d·nm) is the intensity weighted mean hydrodynamic size (mean ± SD)

CHO carbohydrate, *ED* energy density, *PC700* phospholipid concentrate 700 (dairy emulsifier), *PDI* polydispersity index, *PS* particle size, *%en* percentage of total energy

[a]SPE: 2.4 g dairy lipid plus 0.6 g PC700, plus 7 g water (111 kJ)

[b]LPE: 2.8 g dairy lipid plus 0.2 g PC700, plus 7 g water (110 kJ); NE: 2.4 g dairy lipid plus 0.6 g PC700, plus 7 g water (111 kJ)

VAS questionnaire comprised: 'How hungry do you feel?', 'How full do you feel?', 'How satisfied do you feel?' and 'How much do you think you can eat now?' Paper questionnaires were used, and participants placed a line on the 100-mm scale, which were anchored by statements; 'I am not hungry at all/I am not full at all/I am completely empty/nothing at all' on the left and 'I am as hungry I have ever been/I am totally full/I cannot eat another bite/a large amount' on the right. In addition, ratings of thirst, energy levels, relaxation and nausea were also recorded using VAS. Measurements began when fasted prior to the test breakfast (−5 min), continued immediately after the breakfast at 15 min, and then consecutively at 30, 45, 60, 90, 120, 150, 180 (*ad libitum* lunch), 210, 240, 270 and 330 min. Immediately following both the breakfast and the lunch meal participants rated the palatability of the foods, with VAS questions including pleasantness, visual appeal, smell, taste, aftertaste and overall palatability. These questions were anchored (left) by 'not at all pleasant (pleasantness)/bad (visual appeal, smell, taste, palatability)/none (aftertaste)' and (right) by 'as pleasant as I have ever tasted (pleasantness)/good (visual appeal, smell, taste, palatability)/much (aftertaste)'. Participants completed the VAS questionnaires alone, with no interaction with other study participants.

Ad libitum lunch

The *ad libitum* lunch comprised a beef casserole served with boiled white rice, plus water. We have previously shown a single item meal to be as sensitive to prior preload manipulation as a more complex multi-item buffet style meal [34]. Participants confirmed their liking of the meal items at screening. Those following a vegetarian or vegan diet were unable to participate in the study. Food items were presented separately and in sufficient quantity to ensure that participants would not empty the bowl. Participants were provided with instructions to eat from the lunch meal until they felt 'comfortably full'. They were informed that they may eat as much or little as they chose. All participants remained within the individual meal booths during the lunch phase. The composition of the lunch items is presented in Table 2. The meal items were weighed immediately prior to serving to the participant, and again at the end of the meal (Sartorius AG, Goettingen, Germany). The energy and macronutrient content of the lunch meal was again calculated using FoodWorks diet programme, as described above.

Statistical analysis

VAS data on subjective appetite-related feelings were analysed using repeated measures linear mixed model ANOVA

Table 2 Energy and macronutrient composition of *ad libitum* lunch meal

	Weight (g)	Energy (kJ)	ED (kJ/g)	Fat (g)	Fat (%en)	CHO (g)	CHO (%en)	Protein (g)	Protein (%en)
Beef casserole	1646	4204	2.6	41	37	59	22	96	38
Rice, white, boiled	933	5880	6.3	4	3	314	84	26	8
Water, bottled	1500	0	0	0	0	0	0	0	0

ED energy density, *CHO* carbohydrate, *%en* percentage of energy

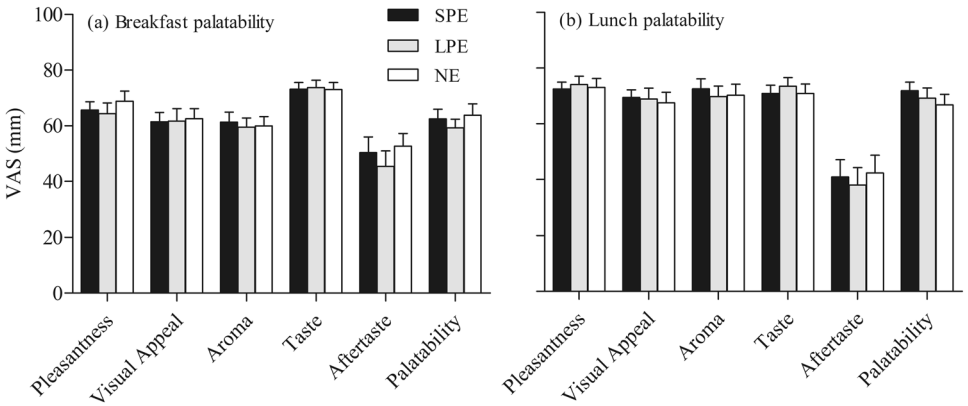

Fig. 2 Mean (SEM) visual analogue scale (VAS) ratings for pleasantness, visual appeal, smell, taste, aftertaste and palatability of **a** breakfast, **b** *ad libitum* lunch meal for each of the three treatments. No significant differences were detected. Small particle size emulsion (SPE), large particle size emulsion (LPE), non-emulsion (NE)

(SAS: PROC MIXED, v8.0 2001, SAS Institute Inc, NC, USA) to account for the cross-over design. The participant, the study arm (emulsion, non-emulsion), the visit number (visit 1, 2, 3) and time point were all included in the model. The diet×time interaction investigated postprandial trajectory of VAS following the breakfast meal and compared between the three study arms. Baseline values were included as a covariate in the analysis. VAS was analysed over the 180 min (3 h; $VAS_{0–3\ h}$) between the breakfast and the lunch meal as well as for the full duration of the study day (330 min, 5.5 h; $VAS_{0–5.5\ h}$). *Ad libitum* lunch intake data were analysed using repeated measures one-way ANOVA. Power calculations were conducted prior to the study, using data from our previous appetite studies using similar single-day design to provide an estimate of the variance for EI. This showed that with 20 participants, a difference between diet groups of 300 kJ was expected to be statistically significant in this three-arm cross-over study. Statistical significance, $P < 0.05$.

Results

Participants

Twenty (20) participants completed the study, with no drop outs and no missing data. The mean (SD) age was 22 (4) years and mean BMI was 22.2 (1.7) kg/m^2. There was no report of any adverse symptoms by participants following consumption of the tests lipids or at other times throughout the study.

Visual analogue scales

Palatability

There was no difference in VAS-assessed pleasantness, visual appeal, aroma, taste, aftertaste or palatability between the three breakfast meals (Fig. 2, $P > 0.05$). Similarly, VAS-assessed palatability-related parameters did not differ following the lunch meal on each of the three treatment arms ($P > 0.05$).

Hunger, fullness, satisfaction and TOF

Figure 3 shows the change in VAS-assessed hunger, fullness, TOF and satisfaction following each breakfast treatment throughout the study day. There was no significant difference at baseline between the three lipids for any of hunger (mean, SEM: 72.4; 76.4; 69.6; $P > 0.05$, ns), fullness (15.3; 14.2; 16.3; $P > 0.05$, ns), TOF (75.3; 77.3; 69.5; $P > 0.05$, ns) or satisfaction (24.4; 27.6; 25.5; $P > 0.05$, ns), and the 790 kJ breakfast meal significantly altered each of the VAS-rated scores as expected with hunger/TOF decreasing and fullness/satisfaction increasing (time, $P < 0.05$). Following consumption of the matched breakfast smoothies containing the various lipid treatments, LPE tended to suppress the rebound in hunger more than both

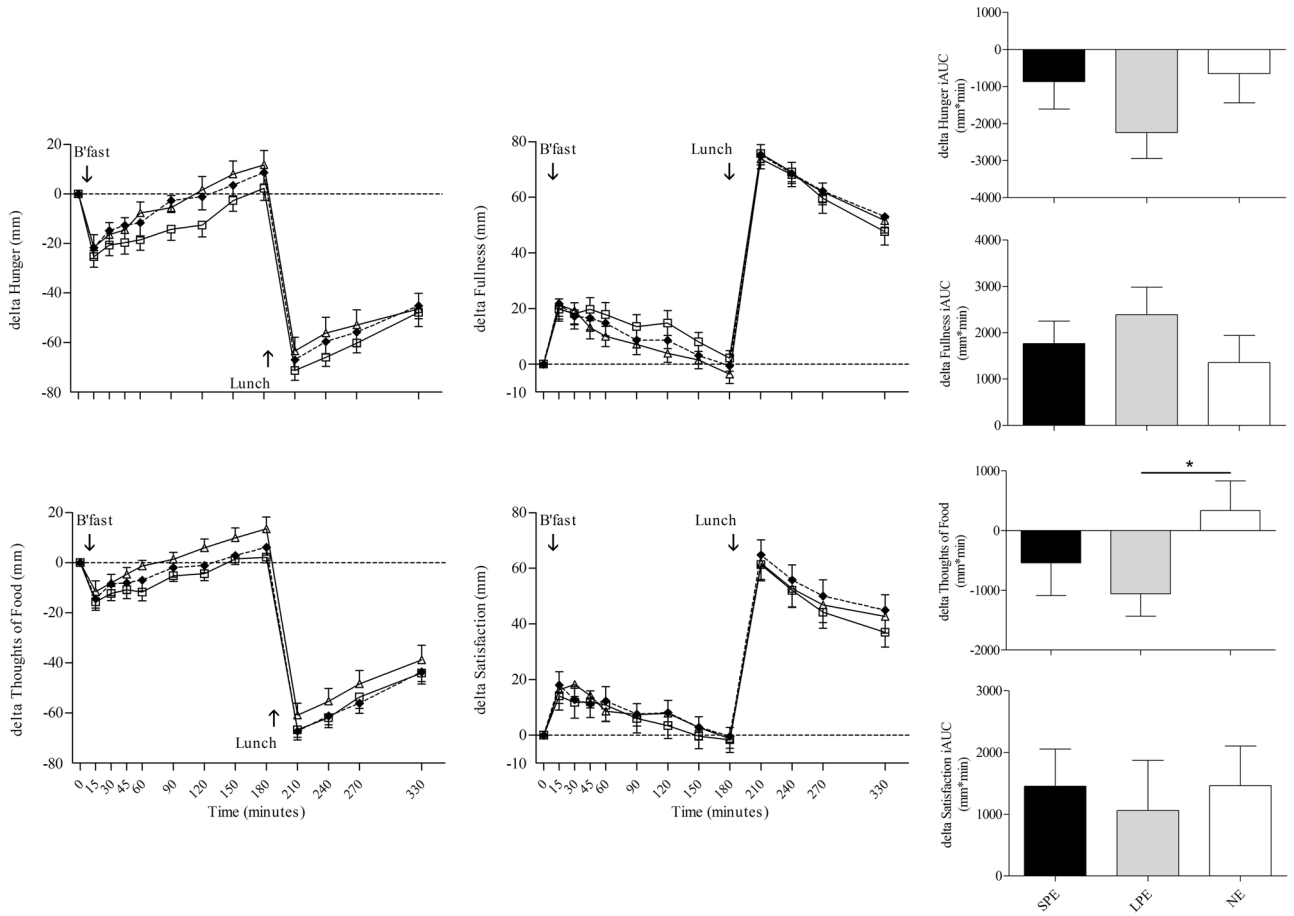

Fig. 3 Change from baseline in hunger, fullness, satisfaction and current thoughts of food (TOF), assessed using visual analogue scale (VAS) ratings. Small particle size emulsion (SPE, ◆), large particle size emulsion (LPE, □), non-emulsion (NE, Δ). Incremental area under the curve calculated as change from fasting baseline (delta iAUC) over 180 min between breakfast and lunch meals are shown as histograms (right-hand panels). Values are presented as mean, SEM. Significantly greater iAUC TOF for LPE vs. NE ($P < 0.05$)

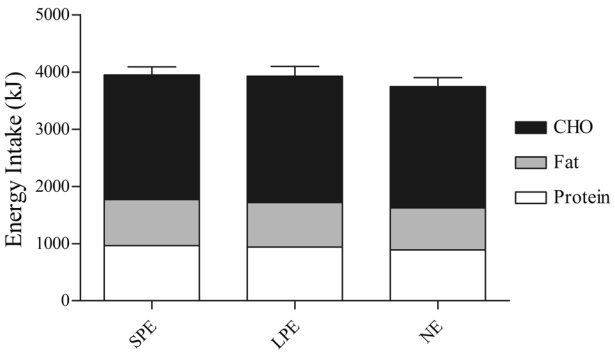

Fig. 4 Mean (SEM) energy and macronutrient intake at the *ad libitum* lunch meal. Small particle emulsion (SPE), large particle emulsion (LPE), non-emulsion (NE)

SPE and the NE control, however, this trend was not significant in this small group study when analysed as change over time (interaction, treatment×time, $P = 0.08$) or incremental area under the curve over 3 h ($iAUC_{0–180\,min}$) between the breakfast and lunch meals, despite LPE suppression of hunger being more than double that of SPE and NE (Fig. 3, right-hand panel, $P = 0.07$; SPE = −872 mm×min, 737 SEM; LPE = −2245 mm×min, 702 SEM; NE = −653 mm×min, 789 SEM). There was a similar pattern for suppression of TOF, where LPE $iAUC_{0\text{-}180\,min}$ was significantly lower than NE control (LPE: −1059 mm×min, 374 SEM; NE: 333 mm×min, 501 SEM; $P < 0.05$). Corresponding feelings of fullness also tended to be higher for LPE compared with the other two treatments, but again did not reach statistical significance (treatment×time, $P = 0.24$).

Ad libitum EI at lunch

Ad libitum EI and macronutrient intake at the lunch meal is presented in Fig. 4. EI at lunch was 3948 (140 SEM) kJ, 3926 (171 SEM) kJ and 3746 (158 SEM) kJ for SPE, LPE and NE, respectively, with no significant difference between the three lipids ($P > 0.05$). Despite the trend towards changes in VAS-rated hunger, fullness and TOF following

LPE, there was no detectable difference between either of the two emulsion treatments (LPE vs. SPE, $\delta = -22$ kJ), SPE and control (SPE vs. NPE, δ=+202 kJ), or LPE and control (LPE vs. NE, $\delta = +180$ kJ). No differences in *ad libitum* macronutrient intake at the lunch was observed between any lipids (all, $P > 0.05$).

Discussion

In our current study, there was no evidence of a suppression of *ad libitum* intake at a meal consumed 3 h after the test breakfast by either of the high-PL lipid emulsions relative to the matched NE lipid control. However, there were some weak effects of LPE on subjective VAS-assessed appetite response in the immediate postprandial phase, although not of sufficient magnitude to provide conclusive evidence. LPE induced a trend towards suppression of hunger, increase in fullness and a significant suppression in TOF relative to the NE control when analysed as change from baseline over 3 h post breakfast. While this clearly was not a strong effect, it cannot be entirely disregarded. There was no evidence to support our primary hypothesis that decreasing the lipid droplet size would promote greater changes in eating behaviour and suppress EI. Underpinning that hypothesis was the premise that consumption of a small-PS high-PL emulsion would activate either the duodenal/jejunal or the ileal brake mechanism as a consequence of protection of the central core lipids from rapid lipolysis by the surrounding surface polar lipids.

Tube feeding studies have provided evidence of a duodenal, jejunal and ileal brake [6, 7, 11, 35–38], all of which are proposed to act by stimulating a feedback loop to gastrointestinal and appetite responses. These enteral studies have shown that the brake is stimulated by nasoileal feeding of lipid into the distal small intestine [6, 7, 9–11, 38]. If high-PL lipid emulsions can remain intact when consumed within a meal and then bypass uptake by the proximal regions of the intestine [3, 18] they may also successfully promote the brake effect. Greater exposure of dietary fat within the lumen of the distal ileum, which would not usually see these nutrients, may cause feedback which inhibits motility in the proximal gut, and slows effects such as gastric emptying and transit within the intestine, potentially also promoting secretion of gut peptides from the ileum. Together, this may alter appetite sensations and feeding behaviour. It is notable, however, that despite considerable evidence of emulsions causing a suppression of food intake relative to energy matched non-emulsified lipids [15–17, 39, 40], there is little mechanistic evidence to explain these effects when dietary lipids are consumed.

Lipid droplets of varying sizes are reported to be metabolised differently as a result of changes in surface area available for lipase activity during lipid digestion [28]. Tube feeding studies in animal models [41] as well as healthy volunteer participants [6, 7] have shown that decreasing the PS of lipid/water emulsions that are delivered directly into the duodenum can alter the response of the GI tract, as well as various aspects of appetite control. For example, small PS (0.260 μm) emulsions have been shown to increase GI peptide secretion as well as suppress hunger and promote fullness relative to much larger PS (30 μm, 170 μm) lipids [6]. Similar findings have also been reported by Maljaars et al. in tube feeding studies, where very small PS (0.880 μm) lipid particles were shown to significantly decrease hunger and increase fullness when compared to far larger-PS (15.5 μm) lipids [7], although again this was as a result of duodenal rather than ileal infusion. In the more recent dietary study, which assessed GI-related outcomes using MRI as well as food intake in a small group of 11 healthy men and women [27], a significant 11% decrease in EI was observed when a very small-PS (0.400 μm) emulsion was compared with a far larger-PS (6 μm) lipid. Using a similar design to that of our current study, they also measured EI at a single outcome lunch meal. In this study, the lipid emulsion was a high sunflower oil (20%) product, which was emulsified using Tween 20 (1%). Ohlsson and colleagues also reported a significant change in satiety-related GI peptides and decrease EI [26] when comparing a very small PS emulsion (0.100 μm) comprising high polar lipid oat oil with larger-PS milk fat globule (1.00 μm). The PS in our current study was selected based on both the previous trials by Burns et al. [15–17], who had observed significant effects of Fabuless with very small PS diameter of 0.08 μm, and this more recent study by Ohlsson et al. with similar very small PS of 0.100 μm. Hence our comparison of dairy fat emulsions of 0.29 and 0.76 μm, which was close to threefold increase in particle diameter and expected to significantly alter GI response, with a non-emulsified control.

The small and statistically non-significant changes in VAS-assessed sensations of hunger and fullness, and also the failure to observe a decrease in EI between either of the emulsions and the NE control in this current study arguably may be caused by small number of male participants. The study was carefully designed and conducted under rigorous and well-controlled conditions and followed established guidelines for short-term measurement of food intake and appetite responses [30]. Twenty male participants completed the study, which in turn was powered to detect a decrease of ~10% of lunch meal intake using a pre-specified *post hoc* pair-wise analysis. The differential observed between LPE, SPE and NE in our trial not only was far less than this and but in fact favoured suppression of intake by the NE control relative to LPE and SPE (−4% and −5%), respectively. There is always a concern about the delivery format for lipid emulsions, with several trials showing that

processing can ameliorate otherwise-significant responses [20]. Since lipid emulsions may be unable to withstand common manufacturing processes, such as thermal and/or shear processing, in our current study the emulsions were consumed within an unprocessed yoghurt format, as used in the early successful Fabuless® trials [15–17, 40] and in the recent oat liposome study from the research team of Ohlsson [26]. We have also previously shown that the format in which emulsions are consumed can be important [23]. Since dairy yoghurt is a specialised acid fermented product, we intended to mimic the conditions by which the emulsions were delivered based on previous clinical studies that had shown significant appetite effects.

Conclusion

There was no evidence from this investigation of short-term appetite response that either small or large PS high-PL lipid emulsions were able to significantly and consistently alter post-meal self-reported ratings of hunger or fullness. While suppression of TOF by the large droplet emulsion relative to the control lipid was observed when analysed as a change from baseline, this was not a strong effect although it cannot be entirely disregarded. In addition, there no was evidence that either of these two emulsions could suppress *ad libitum* food intake relative to the energy matched non-emulsified lipid.

Acknowledgements We thank Eddie Yao and Sally Xiong for preparation and analysis of lipid emulsion PS and stability. Dr Anne-Thea McGill, Sunnie Xin, Cathy Zhong and Shelley Baty assisted in the conduct of the trial. Funding for this intervention study was provided by LactoPharma, New Zealand. Fonterra Co-operative provided ingredients for preparation of the lipid/water emulsions.

Author contributions S.D.P.: Principal investigator, protocol design, data analysis and interpretation, lead writer for manuscript. S.C.B.: Statitican analysis of the data set. A.K.M.: Preparation of lipid products. S.-Y.Q.: Oversight of development and preparation of emulsion, analysis of lipid particle size. S.K.: Manuscript preparation. K.R.W.: Trial manager, recruitment, screening and conduct of study.

Compliance with ethical standards

Conflict of interest S.D.P. is the Fonterra Chair of Human Nutrition, University of Auckland, New Zealand. A.K.M. is an employee of Fonterra Co-operative Group, New Zealand. The remaining authors declare that they have no competing interests

References

1. Mela DJ, Boland MJ Applying structuring approaches for satiety: challenges faced, lessons learned. In: Boland M, Golding M, Singh H, editors. Food structures, digestion and health. London: Elsevier Inc; 2014. p. 363–88.
2. Maljaars PWJ, Keszthelyi D, Masclee AAM. An ileal brake-through? Am J Clin Nutr. 2010;92:467–8.
3. Knutson L, Koenders DJPC, Fridblom H, Viberg A, Sein A, Lennernäs H. Gastrointestinal metabolism of a vegetable-oil emulsion in healthy subjects. Am J Clin Nutr. 2010;92:515–24.
4. Maljaars PWJ, Peters HPF, Mela DJ, Masclee AAM. Ileal brake: a sensible food target for appetite control. A review. Physiol Behav. 2008;95:271–81.
5. Shin HS, Ingram JR, McGill AT, Poppitt SD. Lipids, CHOs, proteins: can all macronutrients put a 'brake' on eating? Physiol Behav. 2013;120:114–23.
6. Seimon RV, Wooster T, Otto B, Golding M, Day L, Little TJ, et al. The droplet size of intraduodenal fat emulsions influences antropyloroduodenal motility, hormone release, and appetite in healthy males. Am J Clin Nutr. 2009;89:1729–36.
7. Maljaars PWJ, van der Wal RJP, Wiersma T, Peters HPF, Haddeman E, Masclee AAM. The effect of lipid droplet size on satiety and peptide secretion is intestinal site-specific. Clin Nutr. 2012;31:535–42.
8. Maljaars J, Romeyn EA, Haddeman E, Peters HPF, Masclee AAM. Effect of fat saturation on satiety, hormone release, and food intake. Am J Clin Nutr. 2009;89:1019–24.
9. Maljaars PWJ, Peters HPF, Kodde A, Geraedts M, Troost FJ, Haddeman E, et al. Length and site of the small intestine exposed to fat influences hunger and food intake. Br J Nutr. 2011;106:1609–15.
10. Maljaars PWJ, Symersky T, Kee BC, Haddeman E, Peters HPF, Masclee AAM. Effect of ileal fat perfusion on satiety and hormone release in healthy volunteers. Int J Obes. 2008;32:1633–9.
11. Van Avesaat M, Troost FJ, Ripken D, Hendriks HF, Aam M. Ileal brake activation: macronutrient-specific effects on eating behavior? Int J Obes. 2015;39:235–43.
12. Poppitt SD, Shin HS, McGill AT, Budgett S, Lo K, Pahl M, et al. Duodenal and ileal glucose infusions differentially alter gastrointestinal peptides, appetite response and food intake: a tube feeding study. Am J Clin Nutr. 2017;106:1–11.
13. Alleleyn AME, Van Avesaat M, Troost FJ, Masclee AAM. Gastrointestinal nutrient infusion site and eating behavior: Evidence for a proximal to distal gradient within the small intestine? Nutrients. 2016;8:117.
14. Le Roux CW, Aylwin SJB, Batterham RL, Borg CM, Coyle F, Prasad V, et al. Gut hormone profiles following bariatric surgery favor an anorectic state, facilitate weight loss, and improve metabolic parameters. Ann Surg. 2006;243:108–14.
15. Burns AA, Livingstone MBE, Welch RW, Dunne A, Robson PJ, Lindmark L, et al. Short-term effects of yoghurt containing a novel fat emulsion on energy and macronutrient intakes in non-obese subjects. Int J Obes. 2000;24:1419–25.
16. Burns AA, Livingstone MBE, Welch RW, Dunne A, Reid CA, Rowland IR. The effects of yoghurt containing a novel fat emulsion on energy and macronutrient intakes in non-overweight, overweight and obese subjects. Int J Obes. 2001;25:1487–96.
17. Burns AA, Livingstone MBE, Welch RW, Dunne A, Rowland IR. Dose-response effects of a novel fat emulsion (Olibra™) on energy and macronutrient intakes up to 36h post-consumption. Eur J Clin Nutr. 2002;56:368–77.
18. Haenni A, Sundberg B, Yazdanpandah N, Viberg A, Olsson J. Effect of fat emulsion (Fabuless) on orocecal transit time in healthy men. Scand J Gastroenterol. 2009;44:1186–90.
19. Logan CM, McCaffrey TA, Wallace JMW, Robson PJ, Welch RW, Dunne A, et al. Investigation of the medium-term effects of Olibra™ fat emulsion on food intake in non-obese subjects. Eur J Clin Nutr. 2006;60:1081–91.
20. Smit HJ, Keenan E, Kovacs EMR, Wiseman SA, Peters HPF, Mela DJ, et al. No efficacy of processed Fabuless (Olibra) in

suppressing appetite or food intake. Eur J Clin Nutr. 2011;65:81–86.
21. Diepvens K, Steijns J, Zuurendonk P, Westerterp-Plantenga MS. Short-term effects of a novel fat emulsion on appetite and food intake. Physiol Behav. 2008;95:114–7.
22. Smit HJ, Keenan E, Kovacs EMR, Wiseman SA, Mela DJ, Rogers PJ. No appetite efficacy of a commercial structured lipid emulsion in minimally processed drinks. Int J Obes. 2012;36:1222–8.
23. Chan YK, Strik CM, Budgett SC, McGill AT, Proctor J, Poppitt SD. The emulsified lipid Fabuless (Olibra) does not decrease food intake but suppresses appetite when consumed with yoghurt but not alone or with solid foods: a food effect study. Physiol Behav. 2012;105:742–8.
24. Poppitt SD, Han S, Strik CM, Kindleysides S, Chan YK. Investigating acute satiation and meal termination effects of a commercial lipid emulsion: a breakfast meal study. Physiol Behav. 2015;152:20–25.
25. Chan YK, Budgett SC, MacGibbon AK, Quek SY, Kindleysides S, Poppitt SD. Small particle size lipid emulsions, satiety and energy intake in lean men. Physiol Behav. 2017;169:98–105.
26. Ohlsson L, Rosenquist A, Rehfeld JF, Harrod M. Postprandial effects on plasma lipids and satiety hormones from intake of liposomes made from fractionated oat oil: two randomized crossover studies. Food Nutr Res. 2014;58:24465.
27. Hussein MO, Hoad CL, Wright J, Singh G, Stephenson MC, Cox EF, et al. Fat emulsion intragastric stability and droplet size modulate gastrointestinal responses and subsequent food intake in young adults. J Nutr. 2015;145:1170–7.
28. Favé G, Coste TC, Armand M. Physicochemical properties of lipids: new strategies to manage fatty acid bioavailability. Cell Mol Biol. 2004;50:815–31.
29. Armand M, Pasquier B, André M, Borel P, Senft M, Peyrot J, et al. Digestion and absorption of 2 fat emulsions with different droplet sizes in the human digestive tract. Am J Clin Nutr. 1999;70:1096–106.
30. Blundell J, De Graaf C, Hulshof T, Jebb S, Livingstone B, Lluch A, et al. Appetite control: methodological aspects of the evaluation of foods. Obes Rev. 2010;11:251–70.
31. Poppitt SD, Strik CM, MacGibbon AKH, McArdle BH, Budgett SC, McGill AT. Fatty acid chain length, postprandial satiety and food intake in lean men. Physiol Behav. 2010;101:161–7.
32. Poppitt SD, Strik CM, McArdle BH, McGill AT, Hall RS. Evidence of enhanced serum amino acid profile but not appetite suppression by dietary glyco-macropeptide (GMP): a comparison of dairy whey proteins. J Am Coll Nutr. 2013;32:177–86.
33. Shin HS, Kindleysides S, Yip W, Budgett SC, Ingram JR, Poppitt SD. Postprandial effects of a polyphenolic grape extract (PGE) supplement on appetite and food intake: a randomised dose-comparison trial. Nutr J. 2015;14:96.
34. Wiessing KR, Xin L, McGill AT, Budgett SC, Strik CM, Poppitt SD. Sensitivity of ad libitum meals to detect changes in hunger. Restricted-item or multi-item testmeals in the design of preload appetite studies. Appetite. 2012;58:1076–82.
35. Lin HC, Zhao XT, Wang L. Intestinal transit is more potently inhibited by fat in the distal (ileal brake) than in the proximal (jejunal brake) gut. Dig Dis Sci. 1997;42:19–25.
36. Read NW, McFarlane A, Kinsman RI, Bates TE, Blackhall NW, Farrar GBJ, et al. Effect of infusion of nutrient solutions into the ileum on gastrointestinal transit and plasma levels of neurotensin and enteroglucagon. Gastroenterology. 1984;86:274–80.
37. Spiller RC, Trotman IF, Higgins BE, Ghatei MA, Grimble GK, Lee YC, et al. The ileal brake - inhibition of jujunal motility after ileal fat perfusion in man. Gut. 1984;25:365–74.
38. Welch I, Saunders K, Read NW. Effect of ileal and intravenous infusions of fat emulsions on feeding and satiety in human volunteers. Gastroenterology. 1985;89:1293–7.
39. Hursel R, Westerterp-Plantenga M. The effects of a novel fat emulsion (Olibra/Fabuless TM) on energy intake, satiety, weight loss, and weight maintenance. Oxford, UK: Blackwell Publishing; 2010.
40. Diepvens K, Soenen S, Steijns J, Arnold M, Westerterp-Plantenga M. Long-term effects of consumption of a novel fat emulsion in relation to body-weight management. Int J Obes. 2007;31:942–9.
41. Borel P, Armand M, Pasquier B, Senft M, Lafont H, Lairon D, et al. Digestion and absorption of tube-feeding emulsions with different droplet sizes and compositions in the rat. J Parenter Enteral Nutr. 1994;18:534–43.