Impact of isocaloric exchanges of carbohydrate for fat on postprandial glucose, insulin, triglycerides, and free fatty acid responses-a systematic review and meta-analysis

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Published in:
European Journal of Clinical Nutrition

DOI:
10.1038/s41430-019-0534-6

Publication date:
2020

European Journal of Clinical Nutrition (2020) 74:1–8
https://doi.org/10.1038/s41430-019-0534-6

REVIEW ARTICLE

Impact of isocaloric exchanges of carbohydrate for fat on postprandial glucose, insulin, triglycerides, and free fatty acid responses—a systematic review and meta-analysis

Anoush Kdekian[1,2] · Marjan Alssema[1] · Eline M. Van Der Beek[2,3] · Arno Greyling[1] · Mario A. Vermeer[1] · David J. Mela[1] · Elke A. Trautwein[1]

Received: 18 August 2019 / Revised: 6 November 2019 / Accepted: 12 November 2019 / Published online: 25 November 2019

Abstract

Varying the macronutrient composition of meals alters acute postprandial responses, but the effect sizes for specific macronutrient exchanges have not been quantified by systematic reviews. Therefore the aim is to quantify the effect size of exchanging fat for carbohydrates in mixed meals on postprandial glucose (PPG), insulin (PPI), triglycerides (PPTG), and free fatty acids (PPFFA) responses by performing a systematic review and meta-analysis of randomized controlled trials. A systematic literature search was undertaken on randomized controlled trials comparing isocaloric high fat with high carbohydrate meals, with comparable protein contents and at least one postprandial glycemic- and one lipid outcome. The outcome data were extracted and expressed as mean postprandial levels over 2 h. Ten studies involving 14 comparisons met the eligibility criteria. Data were available for meta-analysis from 347 participants, consuming mixed meals containing 250–1003 kcal, and total fat contents of 33.3–75.6 percentage of energy (en%) (intervention) versus 0–31.7 en% (control). Each 10en% increase in fat, replacing carbohydrates produced a mean reduction in PPG of 0.32 mmol/l (95% CI −0.64 to −0.00, $p = 0.047$), a reduction in PPI of 18.2 pmol/l (95% CI −24.86 to −11.54), an increase in PPTG of 0.06 mmol/l (95% CI 0.02 to 0.09, $p = 0.004$), with no statistically significant effect on PPFFA. Modest exchange of carbohydrates for fats in mixed meals significantly reduces PPG and PPI and increases PPTG responses. The quantitative relationships derived here may be applied to predict responses, and to design and optimize meal macronutrient compositions in dietary intervention studies.

Introduction

The macronutrient composition of the diet is part of most dietary recommendations, largely supported by evidence of how this can influence the risk of noncommunicable diseases [1]. However, there is limited quantitative underpinning for strict, specific macronutrient reference values. Indeed, American (2015) [2] as well as European (2010) [3] guidelines give broad reference ranges rather than exact reference values (20–35 en% for total fat and 45–65 en% for total carbohydrate). Yet, the benefits and drawbacks of higher-fat (HF) versus higher-carbohydrate (HC) diets are still a topic of scientific debate [4].

Several reviews and meta-analyses have compared the long-term effects of HF versus HC diets, suggesting different possible health benefits depending on the specific outcomes considered [5–10]. It is clear that different macronutrients elicit different postprandial responses [11]. Dietary fat elicits the TG response while carbohydrates primarily elicit glucose and insulin responses [12]. The postprandial response may be an intermediary metabolic pathway in the relationship between dietary macronutrient composition and longer-term health benefits. Elevated postprandial glucose and lipid responses are associated with

Supplementary information The online version of this article (https://doi.org/10.1038/s41430-019-0534-6) contains supplementary material, which is available to authorized users.

✉ Anoush Kdekian
a.kdekian@umcg.nl

[1] Unilever Research and Development, Vlaardingen, The Netherlands

[2] University Medical Centre Groningen, Groningen, The Netherlands

[3] Danone Nutricia Research, Utrecht, The Netherlands

increased oxidative stress, inflammation, and reduction in antioxidant defenses [13].

The magnitude of postprandial responses to mixed meals depends largely on the total amount of ingested fat and carbohydrates. However, when comparing meals with the same caloric content, the relative amounts of fat and carbohydrates in the meal are more relevant and might potentially also determine the postprandial response. These isocaloric exchanges of fats and carbohydrates would provide a route for intervention and a means to reduce undesirable effects associated with high glucose and lipid responses after a meal. The quantitative effects of specific variations in the amount of fat relative to carbohydrate in a mixed meal on overall postprandial metabolism is largely unknown. Therefore, the aim of this study was to perform a systematic review and a meta-analysis of randomized controlled trials to determine on the quantitative effects of isocaloric exchanges of total carbohydrates for total fat on postprandial glucose (PPG), insulin (PPI), TG (PPTG) and FFA (PPFFA) responses. The meta-regression approach used here provides an estimate of effects of the fat for carbohydrate exchange over a continuous range at similar intakes of energy and protein.

Methods

Eligibility criteria and search strategy

A systematic literature search was executed according to preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines [14]. The study protocol was registered in Prospero with registration number CRD42018081516. Electronic databases Pubmed, Scopus and, Ovid FSTA were searched for relevant papers until February 11th, 2019. Inclusion criteria were randomized control trials with humans older than 18 years, an intervention consisting of a mixed meal high in total fat, a comparator consisting of a mixed meal high in carbohydrates, less than 10% difference in total energy, less than 20en% difference in proteins and at least one outcome for glucose/insulin metabolism (PPG or PPI) and at least one for the lipid metabolism (PPTG or PPFFA). Studies with pregnant or lactating women or people using glucose or lipid lowering medication were excluded, as well as interventions that specifically included omega three fatty acids. The minimum duration of the postprandial measurements was 120 min, but studies that reported fewer than three measurements in this period were excluded. Postprandial measurements for TG and FFA were cutoff to a maximum of 240 min. The search applied a range of different keywords for type of intervention (e.g., "fat load', "mixed meal"), outcome measure (e.g. "postprandial", "area under the curve") and study design (e.g. "crossover" and "randomized"). The full search string can be found in supplement 1. After the search, duplicates were removed and titles and abstracts were screened for potential eligibility, by two researchers independently. Pairs of researchers (AK, MA, AG, MAV, DJM, EAT) screened an agreed number of records and the subsequent full text screening was also done independently by pairs of these researchers. Inconsistencies between assessors were resolved by consensus.

Data extraction and risk of bias assessment

Data on the publication, study design and procedures, meal test composition and postprandial measurements were extracted from eligible publications by one researcher (AK) and checked by two others (MAV and MA). Total and incremental AUC's for 120 min (glucose and insulin) and 120–240 min (triglycerides and FFA) were extracted from the eligible studies. Where necessary, AUC data reported as figures, were estimated using 'Excel TM image to data' [15]. Where AUC's for given time periods were not given in text or in figure, mean values at individual postprandial time points were extracted and used to calculate AUC (see 'data synthesis' below). Quality of each trial was scored independently by two researchers (AK, MA, MAV) based on the criteria of Jadad et al. because of its reproducibility [16, 17]. Using this method, studies were assigned 0 or 1 point for each of 11 criteria (thus a maximum total score 11 points): randomization, blinding, description of withdrawals and drop outs, objectives, definition of outcome measures, description of in- and exclusion criteria, justification of the sample size, description of the interventions, control group, description of adverse effects and methods of statistical analysis.

Data synthesis and statistical analysis

Outcome data were standardized for units: mmol/l for glucose, TG and FFA, and pmol/l for insulin. Standard errors (SE) were transformed into standard deviations (SD) ($SE = SD/\sqrt{N}$, where $N =$ number of individuals). In cases where AUC's for given time periods were not reported, mean values at individual time points were used to calculate incremental AUC's, calculated by the trapezoidal method as net incremental AUC [18]. The AUC was calculated up to 120 min for glucose and insulin and up to 240 min for TG and FFA. Calculation of the variance in iAUC was based on the SD of individual time points by using matrix algebra involving a covariance matrix with the assumed correlation structure being compound symmetry [19]. Assumed correlations between time points were $r = 0.75$ for glucose, $r = 0.5$ for insulin, $r = 0.9$ for TG and $r = 0.5$ for FFA (based on internal data, unpublished).

Absolute outcomes were expressed as mean postprandial levels by dividing the AUC and the SD by time. SE of absolute and relative changes were calculated as earlier described [20], assuming a within subject correlation coefficient of 0.7. Weighted regression analysis were performed using SPSS software version 25.0 (https://developer.ibm.com/predictiveanalytics/2017/11/02/spss-statistics-25-packaging-reference/) [21]. Difference in en% as fat in the meal was the independent and the postprandial outcome measure the dependent variable. Weighing was done for the inverse variance of the difference in outcome between intervention and control $(1/SE(diff)^2$. Subgroup analyses (high vs low study quality, with vs without diabetes, high vs low energy loads) were prespecified to be performed when more than ten comparisons were available for a subgroup (PROSPERO; CRD42018081516).

Results

The literature search retrieved 5327 unique publications of which 485 were selected for full text screening. After the full text screening, ten papers met the eligibility criteria and had data available for inclusion in the quantitative synthesis (Fig. 1) [4, 9, 22–30]. Table 1 presents the main characteristics of the ten studies that are included in this review involving 14 comparisons between total fat and total carbohydrate exchange. A total of 347 participants were included with a range in average age of 23.9–62.5 years, BMI 19.4–29.3 kg/m^2, total meal energy content 250–1003 kcal, and meal fat content of 33.3–75.6 en% in the intervention group and 0–31.7 en% in the comparator group.

Figures 2, 3, 4, and 5 show the absolute changes in PPG, PPI, PPTG, and PPFFA in relation to the difference in en% in the mixed meals based on fats. Each 10en% increase in fat content, exchanged for carbohydrates, was associated with significantly lower PPG (beta −0.32 mmol/l; 95% CI −0.64 to 0.00, $p = 0.047$) and PPI (beta = −18.20 pmol/l; 95% CI −24.86 to −11.54, $p \leq 0.001$), and higher PPTG (beta = 0.06 mmol/l; 95% CI 0.02–0.09, $p = 0.004$). Exchanges of fat for carbohydrate were not associated with significant changes in PPFFA (beta = 0.02 mmol/l; 95% CI −0.07 to 0.10, $p = 0.682$). Subgroup analyses could not be performed as fewer than ten comparisons were available for the prespecified subgroups.

Out of the maximum possible 11 points for quality, scores were uniformly low, with no study scoring more than four points (supplement 2). Almost all papers failed to adequately report if the study was double blind (seven papers), the description of withdrawals (seven papers), justification of sample size (eight papers) and a methodological description used to assess adverse effects (eight papers). All studies reported if the study was randomized, the definition of outcome measures, a clear description of the in- and exclusion criteria, a control group and a description on statistical analysis methods.

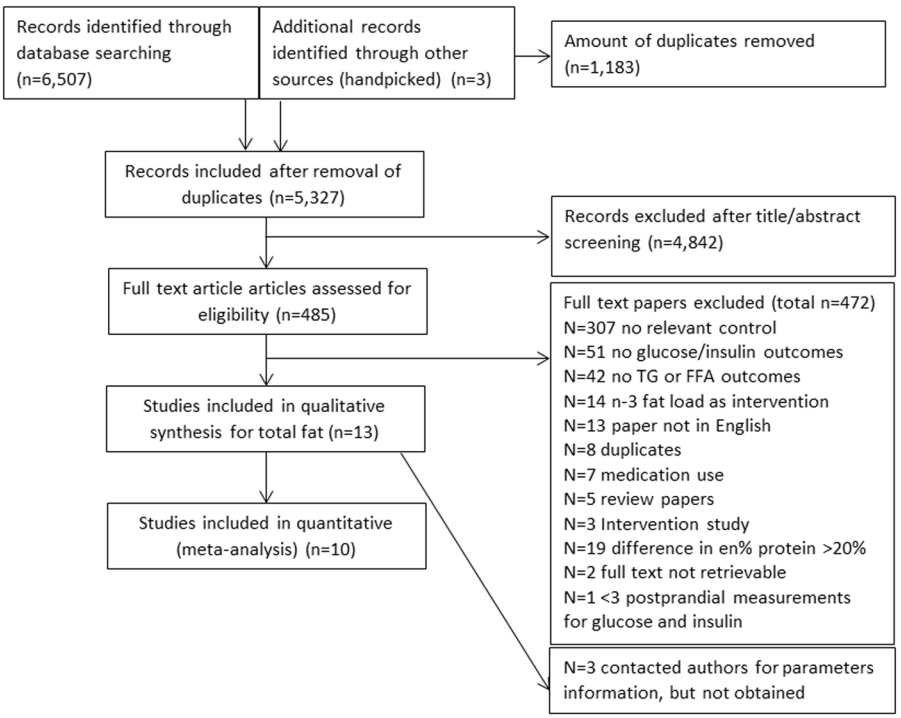

Fig. 1 PRISMA flowchart for eligibility

Table 1 Study characteristics.

Reference	Participants characteristics	Study design and health state	Intervention kcal for total energy and en% from macronutrients	Comparator kcal for total energy and en% from macronutrients	Postprandial time points in min
Dandona et al. [22]	$N = 10$ Male and female Age: 33 BMI: NR Weight: NR	Crossover, healthy	Kcal: 910 Fats: 42.5 Carbohydrates: 40.9 Proteins: 17	Kcal: 910 Fats: 27.3 Carbohydrates: 58 Proteins: 14.9	Glucose and insulin: 15, 30, 45, 60, 75, 90, 120 Free fatty acids: 15, 30, 45, 60, 75, 90, 120, 180
Haimoto et al. [23]	$N = 31$ Male and female Age: 62 BMI: 23.2 Weight: NR	Crossover, diabetes type 2	Kcal: 500 Fats: 75.6 Carbohydrates: 7.11 Proteins: 18.2	Kcal: 500 Fats: 21.6 Carbohydrates: 59.3 Proteins: 18.7	Glucose, insulin, triglycerides, and free fatty acids: 30, 60, 120
Jung et al. [24] 1st comparison	$N = 32$ Male Age: 23.9 BMI: 21.4 Weight: 64.8	Crossover, healthy	Kcal: 588 Fats: 35.6 Carbohydrates: 43.2 Proteins: 21	Kcal: 586 Fats: 25.7 Carbohydrates: 55.7 Proteins: 18.6	Glucose and insulin: 15, 30, 45, 60, 120 Triglycerides: 15, 30, 45, 60, 120, 240
Jung et al. [24] 2nd comparison	$N = 32$ Male Age: 23.9 BMI: 21.4 Weight: 64.8	Crossover design, healthy	Kcal: 588 Fats: 37.8 Carbohydrates: 43.7 Proteins: 18.7	Kcal: 586 Fats: 25.3 Carbohydrates: 58.2 Proteins: 16.7	Glucose and insulin: 15, 30, 45, 60, 120 Triglycerides: 15, 30, 45, 60, 120, 240
Khoury et al. [25]	$N = 20$ Male Age: 28 BMI: 29 Weight: 90.3	Crossover, metabolic syndrome	Kcal: 566 Fats: 49.9 Carbohydrates: 30 Proteins: 20	Kcal: 566 Fats: 19.9 Carbohydrates: 60.1 Proteins: 20	Glucose and insulin: 15, 30, 60, 120 Triglycerides: 15, 30, 60, 120, 180, 240
Meng et al. [9, 26] 1st comparison	$N = 40$ Male and female Age: 62.5 BMI: 29.3 Weight: NR	Parallel, healthy	Kcal: 250 Fats: 20.2 Carbohydrates: 79.9 Proteins: 0	Kcal: 250 Fat: 0 Carbohydrates: 100 Proteins: 0	Glucose, insulin, triglycerides and free fatty acids: 15, 30, 45, 60, 90, 120
Meng et al. [9, 26] 2nd comparison	$N = 40$ Male and female Age: 62.5 BMI: 29.3 Weight: NR	Parallel, healthy	Kcal: 300 Fats: 33.3 Carbohydrates: 66.7 Proteins in g: 0	Kcal: 300 Fats: 0 Carbohydrates: 100 Proteins: 0	Glucose, insulin, triglycerides and free fatty acids: 15, 30, 45, 60, 90, 120
Meng et al. [9, 26] 3rd comparison	$N = 40$ Male and female Age: 62.5 BMI: 29.3 Weight: NR	Parallel, healthy	Kcal: 400 Fats: 50 Carbohydrates: 50 Proteins: 0	Kcal: 400 Fats: 0 Carbohydrates: 100 Proteins: 0	Glucose, insulin, triglycerides and free fatty acids: 15, 30, 45, 60, 90, 120
Schneeman et al. [27]	$N = 24$ Male and female Age: 35.7 BMI: 24.6 Weight: NR	Crossover, healthy	Kcal: 778 Fats: 37.9 Carbohydrates: 45 Proteins: 16.9	Kcal: 778 Fats: 20 Carbohydrates: 63 Proteins: 16.9	Glucose and insulin: 20, 40, 60, 90, 120 Triglycerides: 20, 40, 60, 90, 120, 180
Shin et al. [4]	$N = 25$ Female Age: 24.5 BMI: 19.4 Weight: 51.5	Parallel, healthy	Kcal: 598.2 Fats: 61.1 Carbohydrates: 24.7 Proteins: 14.2	Kcal: 595.7 Fats: 10.4 Carbohydrates: 75 Proteins: 14.6	Glucose and insulin: 30, 60, 90, 120 Triglycerides and free fatty acids: 30, 60, 90, 120, 240
Van Amelsfoort et al. [28] 1st comparison	$N = 30$ Male Age: 38 BMI: 23.9 Weight: 80	NR, healthy	Kcal: 1003 Fats: 48 Carbohydrates: 37 Proteins: 15	Kcal: 1003 Fats: 28 Carbohydrates: 57 Proteins: 15	Glucose and insulin: 30, 60, 90, 120 Triglycerides and free fatty acids: 30, 60, 90, 120, 240

Table 1 (continued)

Reference	Participants characteristics	Study design and health state	Intervention kcal for total energy and en% from macronutrients	Comparator kcal for total energy and en% from macronutrients	Postprandial time points in min
Van Amelsfoort et al. [28] 2nd comparison	$N = 30$ Male Age: 38 BMI: 23.9 Weight: 80	NR, healthy	Kcal: 1003 Fats: 48 Carbohydrates: 37 Proteins: 15	Kcal: 1003 Fats: 28 Carbohydrates: 57 Proteins: 15	Glucose and insulin: 30, 60, 90, 120 Triglycerides and free fatty acids: 30, 60, 90, 120, 240
Van Schoonbeek et al. [29]	$N = 15$ Male and female Age: NR BMI: 27.8 Weight: NR	Crossover, diabetes type 2	Kcal: 98 Fats: 50 Carbohydrates: 33.1 Proteins: 17	Kcal: 100 Fats: 30.6 Carbohydrates: 54.3 Proteins: 15.2	Glucose and insulin: 15, 30, 45, 60, 75, 90, 120 Triglycerides: 15, 30, 45, 60, 75, 90, 120, 150, 180, 210, 240
Yokoyama et al. [30]	$N = 10$ Male and female Age: 41.4 BMI: 22.9 Weight: NR	Crossover, diabetes type 2	Kcal: 255 Fats: 49 Carbohydrates: 34.2 Proteins: 16.9	Kcal: 250 Fats: 31.7 Carbohydrates: 54.5 Proteins: 14	Glucose and insulin: 30, 60, 90,120, 180 Triglycerides and free fatty acids: 30, 60, 90, 120, 180

NR = not reported

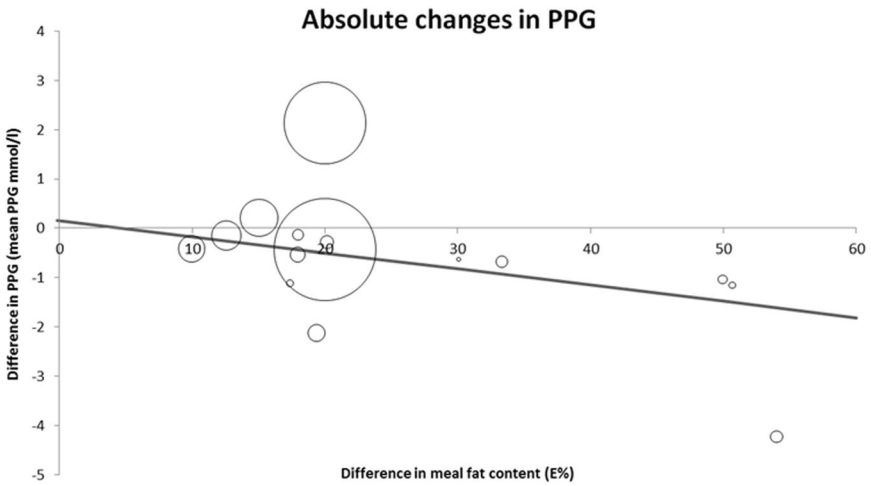

Fig. 2 Difference in mean postprandial glucose response in mmol/l. The bubble size reflects study weight (inverse variance). $y = 0.111–0.032 \times (95\%\ \text{CI} -0.064$ to 0.00, $p = 0.047)$

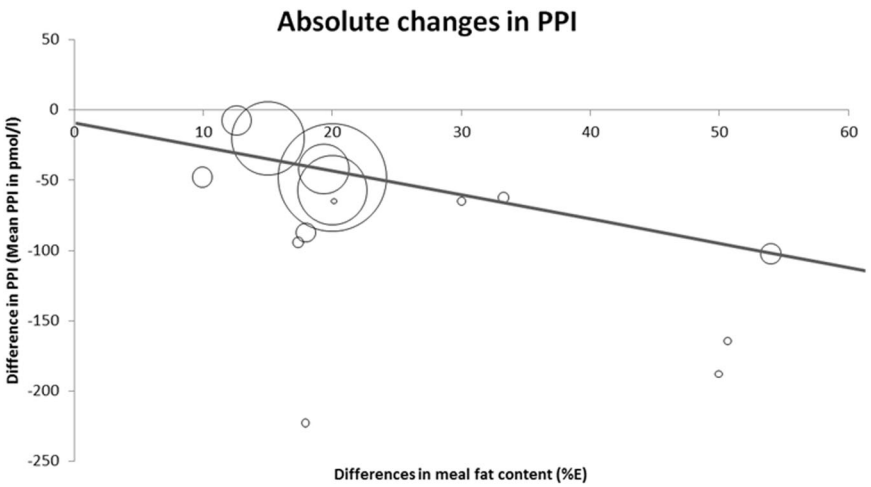

Fig. 3 Difference in postprandial insulin responses in pmol/l. The bubble size reflects study weight (inverse variance). $y = -8.573–1.820 \times (95\%\ \text{CI} -2.486$ to -1.154, $p \le 0.001)$

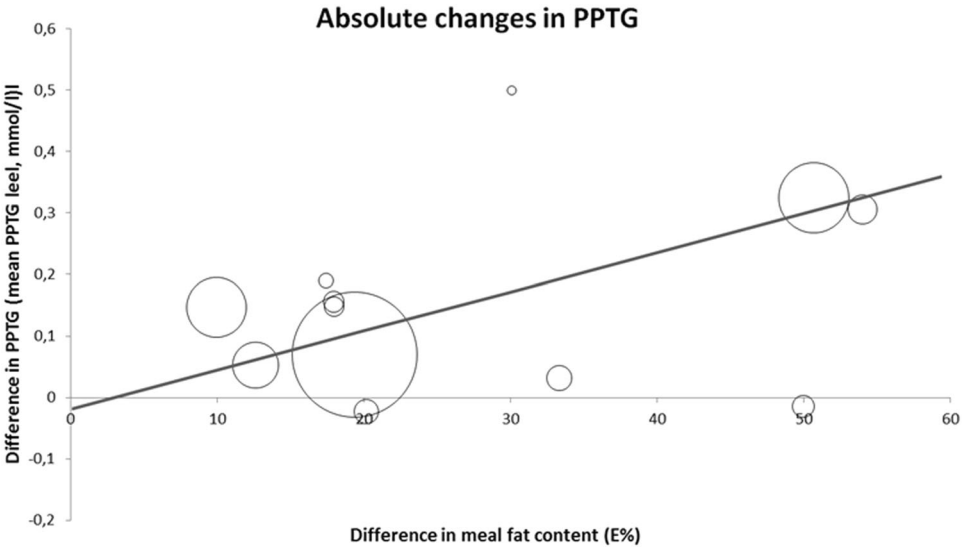

Fig. 4 Difference in postprandial triglyceride responses in mmol/l. The bubble size reflects study weight (inverse variance). $y = -0.011 + 0.006 \times$ (95% CI 0.002–0.009, $p = 0.004$)

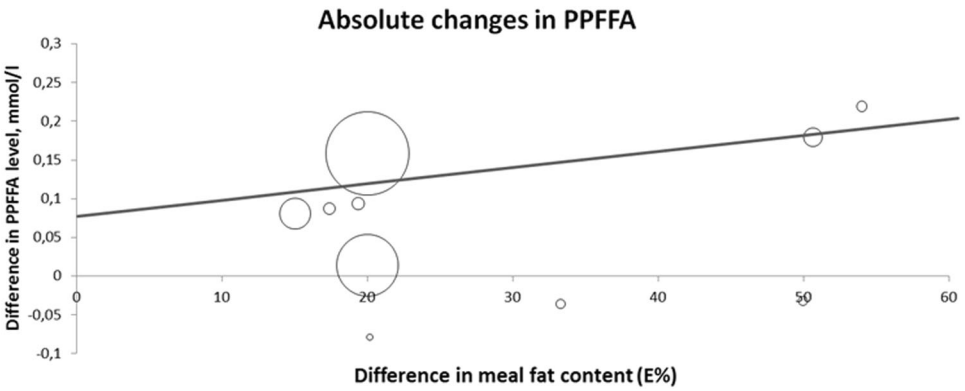

Fig. 5 Difference in postprandial free fatty acid responses in mmol/l. The bubble size reflects study weight (inverse variance). $y = 0.073 + 0.002 \times$ (95% CI − 0.007–0.010, $p = 0.682$)

Discussion

This is the first systematic review that quantifies the effect of isocaloric exchanges of fat and carbohydrates in meals on PPG, PPI as well as PPTG and PPFFA responses. Our analyses show that an HF content in the mixed meals, exchanged for carbohydrates significantly reduced PPG and PPI and increased PPTG. The novelty of the present study is the quantification of the effects of meal fat content on postprandial responses. The divergent effects of increasing fat content of isocaloric meals on postprandial responses, stresses the importance of assessing the effects on both glucose and lipid profile for optimizing meal macronutrient composition.

The health implications of the balancing of these effects may require further evaluation with longer-term studies. For cardiovascular disease outcomes, observational studies have reported the magnitude of the associations with PPG and PPTG measurements. Nielsen et al. studied 4934 men that underwent an oral glucose tolerance test and were followed for 27 years. Data on CVD events and death showed that a difference in 1-h PPG of 2.2 mmol/l was associated with a 10% increase in CVD risk [31]. In the current study we estimated a difference in mean PPG of 0.32 mmol/l when exchanging 10en% carbohydrates for fats. Extrapolating from this using the results from Nielsen et al. for a total diet effect sustains over time, this would translate in a 1–2% lower CVD risk. Mora et al. assessed the relationship of random blood lipid levels and the risk of cardiac outcomes [32]. Results show that a mean increase of 1 mmol/l triglycerides was associated with a 3% increased risk of coronary events (HR 1.03, CI 0.78–1.37). In the current study we estimated a difference in mean PPTG of 0.06 mmol/l per 10en% increase in fat content, which would thus translate in a 0.2% increase in the risk of coronary events. Taken together, these estimates suggest that an increase in fat content exchanged for carbohydrates may have a net protective effect; i.e., for CVD risk, the benefit of the PPG lowering may outweigh the adverse effects of the increases in PPTG have greater protective effects than adverse effects of increases in PPTG. However, more precise evaluation in increasing fat content in meals on longer-term cardiovascular and other outcomes are clearly needed to better understand their overall health effects. One such approach may be a method for integrated evaluation of PPG- and lipid metabolism in terms of disease risk. A review by Emerson

et al. suggested to study the optimal summation of glucose and lipids responses to predict the risk of disease accurately [33]. Such an index may be useful for generating clinical benchmarks for postprandial responses. The current data may be of value in defining and optimizing macronutrient composition in longer-term dietary intervention studies on the basis of given postprandial response benchmarks. Furthermore, the present data can be applied to predict key postprandial metabolic responses to fat and carbohydrate content.

We also observed nonsignificant trend for an increase in PPFFA with HF relative to carbohydrate content. FFA are normally suppressed by insulin and are therefore higher in the fasting state. A significant increase, which means a relatively lower postprandial suppression in FFA was expected when carbohydrates were replaced for fats as less insulin is then released in the blood [34]. The absence of a statistically significant effect of fat for carbohydrate exchange and PPFFA in our analysis may be explained by the high variation of FFA within studies [35].

A strength of this meta-analysis is the inclusion of a modest body of studies with measurements of PPG/insulin levels in combination with a TG/FFA after consumption of mixed meals. Other strengths are the inclusion of only randomized controlled trials administering mixed meals in the fasting state, with closely matched energy and less than 20e% difference in protein content, and a minimum of three postprandial measurements.

The current meta-analysis also has several limitations. First, we did not aim to specify the types of carbohydrates or fats. Therefore our study does not provide information about the effect of carbohydrate and fat quality [36–39]. The amount and type of protein in mixed meals may also affect postprandial meal responses. We excluded studies with differences in proteins larger than 20en%, and did not plan to perform analyses that might have shown differences in metabolic responses with respect to protein content or type. Those analyses may be recommended as a topic for further research. We also did not take analyses based on personalized factors such as sex differences, age, anthropometrics, lifestyle, menopausal status, genetic background, and microbiota, which may differently affect postprandial responses [40–42]. Another limitation and potential future analysis would be consideration of the types of foods consumed as mixed meals, in terms of ingredients or consistency such as liquid versus solid, which is known to have an effect on PPG [43].

Finally, the limited number of studies meeting our predefined inclusion criteria on outcome data (both glucose and lipid responses) precluded conducting our predefined subgroup analyses on study quality, meal energy load or diabetes diagnosis. The prespecified criterion of ten comparisons for subgroup analyses may in retrospect have been overly strict, especially as only ten studies met the inclusion criteria. Also while most data came from meals in the range of 250–600 Kcal, there was a relatively wide spread of energy contents (98–1003 Kcal) in the intervention meals, and we did not prespecify analyses based on this. These additional analyses could explain some sources of variance in responses and would be of interest to consider in further research on this topic.

Conclusion

Modest exchanges of carbohydrates for fats in mixed meals significantly reduces PPG and PPI responses and increases PPTG responses. The quantitative relationships derived here may be applied to predict responses, and to design and optimize meal macronutrient composition in dietary intervention studies.

Acknowledgements The authors thank Harry H Hiemstra, Ewoud A Schuring, Carolien Ruijgrok for their statistical support.

Compliance with ethical standards

Conflict of interest At the time this research was carried out, MA, EAT, DJM, AG, MAV were employees of Unilever, which produces and markets consumer food products, and AK was an MSc student at Unilever and Wageningen University. EvdB is an employee of Danone Nutricia Research.

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