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Reducing postprandial glucose in dietary intervention studies and the magnitude of the effect on diabetes-related risk factors: a systematic review and meta-analysis

---Manuscript Draft---

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Abstract: Purpose: Reducing postprandial hyperglycemia has beneficial effects on diabetes-related risk factors, but the magnitude of the reduction needed to achieve such an effect is unknown. To quantify the relationship of acute glucose and insulin postprandial responses with longer-term effects on diabetes-related risk factors by performing a systematic review and meta-analysis of dietary intervention studies. Methods: We systematically searched EMBASE and MEDLINE. Dietary intervention studies among any human population aiming to reduce postprandial glycaemia, with actual measures of postprandial glucose (PPG) and/or insulin (PPI) as acute exposures (incremental area under the curve, iAUC) as well as markers of glucose metabolism (fasting glucose, HbA1c) and insulin sensitivity (fasting insulin, HOMA-IR) after at least 4 weeks of diet intervention as outcomes, were included. Meta-analyses were performed for the effects on acute exposures and on diabetes-related risk factors. The relationship between changes in acute exposures and changes in risk factor outcomes was estimated by meta-regression analyses. Results: Out of the 13004 screened papers, 14 papers with 14 comparisons were included in the quantitative analysis. The dietary interventions acutely reduced mean...
PPG (mean difference (MD), -0.27 mmol/l; 95% CI, -0.41 to -0.14) but not mean PPI (MD, -7.47 pmol/l; 95% CI, -16.79 to 1.86). No significant overall effects on fasting glucose and insulin. HbA1c was reduced by -0.20% (95% CI -0.35 to -0.05). Changes in acute PPG were significantly associated with changes in fasting plasma glucose (FPG) (per 10% change in PPG: β = 0.085 (95% CI, 0.003, 0.167), k=14), but not with fasting insulin (β = 1.20 (95% CI, -0.32, 2.71), k=12). Changes in acute PPI were not associated with changes in FPG (per 10% change in PPI: β = -0.017 (95% CI, -0.056, 0.022), k=11).

Conclusions: Only a limited number of postprandial glucose lowering dietary intervention studies measured acute postprandial exposures to PPG/PPI during the interventions. In this small heterogeneous set of studies, an association was found between the magnitude of the acute postprandial responses and the change in fasting glucose but no other outcomes. More studies are needed to quantify the relationship between acute postprandial changes and long-term effects on risk factors.

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To Whom It May Concern,

We are hereby resubmitting our manuscript ‘Reducing postprandial glucose in dietary intervention studies and the magnitude of the effect on diabetes-related risk factors: a systematic review and meta-analysis’. We thank reviewers for their careful consideration of the paper and constructive comments. Below we provide point by point responses to reviewers’ comments.

Reviewers’ comments:

Reviewer #1: The manuscript by Ruijgrok et al., titled "Reducing postprandial glucose in dietary intervention studies and the magnitude of the effect on diabetes-related risk factors: a systematic review and meta-analysis" aims to provide a comprehensive meta-analysis on the dietary intervention trials for glucose management. While the topic is very current and relevant, there are concerns that need to be clarified:

1. The search was done until March 2018, which is >1 year ago. Please update.
   We have now updated the search until September 2019. This updated yielded 917 titles, of which 24 were screened full-text and 2 were included in the systematic review and meta-analysis. This is now revised throughout the methods and the results of the paper.

2. This systematic review and meta analysis concerns the acute effect of dietary interventions on postprandial glycemia. There is certainly confusion on behalf of the reader as to the scope of this paper. The reader is under the impression that dietary interventions within a broad scope are being evaluated (ie title and abstract). In the introduction, the authors focus on the low GI/GL foods on postprandial glycemia. Moreover, the search terms are primarily capturing GI/GL as intervention material. The authors end up with 2/13 comparisons evaluating mulberry leaf extract (a dietary supplement) and remaining comparisons of GI/GL.
   If the objective is to quantify postprandial effect of low vs high GI/GL interventions following continued exposure, please adjust the title and abstract objective to more clearly reflect the topic studied, and consider excluding mulberry extract studies. Otherwise, please open the search to all dietary interventions (and/or supplements) and revise the analysis to reflect the aim.
   The reviewer is correct that dietary interventions with a broad scope were evaluated. The search was designed to identify dietary interventions that aimed at reducing acute glycaemic exposures (as an inclusion criterion, and reflected as such in the search term) to investigate their longer term effects on glycaemic markers. This is the reason for having ‘glycaemic’ (not only glycaemic index (MESH)) in the search terms. This could be any diet, food or supplement that induced a reduction in acute glycaemic exposure, either by glycaemic index, load or glycaemic response. Indeed, most of the included studies, the interventions were characterized as low GI/GL, and two were mulberry extract studies. It should be noted that there was a wide variety in low GI/GL diets. The GI/GL interventions comprised the whole diet low GI (LGI) versus high GI (HGI) (6 comparisons), low GI breakfast (1 comparison), type of rice (2 comparisons) and liquid carbohydrate-modified supplement (2

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Cover letter Click here to access/download;Authors’ Response to Reviewers’ Comments;Cover letter Ruijgrok et al 2020.docx
comparisons). To better emphasis the variation in diet types, this is now added in the results section as follows in the methods on page 5, line 107-108: ‘involved any dietary intervention that aimed at reducing GI, GL, or postprandial glucose responses;’

and in the results sections as follows on page 9, line 202-205: ‘Two out of 14 comparisons aimed to reduce postprandial glucose via mulberry leaf extract supplementation [14,19] while the other comparisons were dietary interventions of whole diet low GI (LGI) versus high GI (HGI) (6 comparisons), low GI breakfast (1 comparison), carbohydrate-reduced high-protein diet (1 comparison), type of rice (2 comparisons) and liquid carbohydrate-modified supplement (2 comparisons).’

Other:
3. Line 102 - studies were included if individuals had pre-diabetes. Was this as defined by the individual studies or based on specific criteria/guidelines? Studies among any human population were eligible, therefore definitions for pre-diabetes were not relevant as inclusion criterion. Given the context of the topic it was explained in the paper that ‘any human population’ involved healthy individuals as well as (pre)-diabetes patients (type 1 and type 2 diabetes mellitus) as follows on page 5, line 107: ‘studied any human population, including healthy individuals and individuals with prediabetes, type 1 and type 2 diabetes mellitus’.

4. Line 155 - Random effects method was used if number of comparisons was > 10 however, in Supplementary Figure 4 (C) - there are 6 comparisons listed in the forest plot and random effects method was used. Should this be changed to fixed effects? Line 155 refers to the random effects meta-regression analyses, and not the forest plots in supplementary Figures which are regular meta-analyses. The Cochrane handbook (chapter 9.6.4) was applied for conducting meta-regression analyses, which proposes to only consider meta-regression when there are more than 10 comparisons in a meta-analysis.

5. Line 168-170 - planned subgroup analyses for normal vs abnormal glucose metabolism was not conducted because < 10 comparisons; however based on results below, there are > 10 comparisons for many observations? (i.e. Line 191-194 - “The total number of comparisons retrieved from the included set of papers for the quantitative analyses was 13. For PPG, there were 13 comparisons with outcome FPG, 11 with fasting insulin, and 6 with HbA1c. For PPI, there were 10 comparisons with outcome FPG, 9 for fasting insulin, and 3 for HbA1c.”)
The reviewer is correct that for a number of outcomes there were more than 10 comparisons. For these comparisons a meta-regression was conducted, while this was not performed for the outcomes were there were less than 10 comparisons. However, by creating subgroups of data (studies in normal versus abnormal glucose metabolism) the number of comparisons within one of the subgroups became smaller than 10 comparisons. Therefore meta-regression analyses stratified by subgroup could not be conducted because of the small number of studies.

6. Line 183 - Provide more detail on how papers were found manually ie: Were the references of included studies searched?
The manually identified papers were identified in the process of developing the search string, or were from authors own files. References in included studies were not systematically searched. This is now explained on page 5, line 95-97.

7. Line 260-261 - "Other potential sources of heterogeneity were study quality, duration of the chronic intervention and compliance to diets." Consider exploring these sources of heterogeneity through post hoc analysis. Please include results of the subgroup analysis. We have considered exploring these sources of heterogeneity. However, as for the other subgroups analyses, creating subgroups for these sources of heterogeneity reduced the number of comparisons below 10, which was insufficient for a meta-regression analysis.
8. Supplementary Figure 3 (B) & Supplementary Figure 4 (B) - the scales of these forest plots makes it difficult to see the diamond displaying overall effect
Review manager provides the scaling of the plot automatically and we cannot alter this. However, the overall estimate is displayed next to the diamond for the overall effect, which clarifies the effect size of the diamond.

9. Consider performing sensitivity analysis to determine whether one study exerted particular influence on the results
The heterogeneity in our analyses was generally very low with an I²-square statistic well below 50% for almost all comparisons. Therefore our results are not due to heterogeneity of the effects across studies and a sensitivity analysis to exclude specific studies will not yield different results.

10. Consider using GRADE to evaluate the certainty of the evidence
Thank you for this suggestion. GRADE is a very relevant framework to evaluate evidence for making clinical practice recommendations. However, the research question of our study does not yet provide results that are at a phase to be applied in clinical practice. We have now phrased this as such in our discussion and conclusion without applying the GRADE system for this.

Reviewer #2: MAJOR COMMENTS

Abstract
* Line 37-41 - it is important to indicate the population as part of the inclusion criteria
Agree, this is now added in the paper on page 2 line 38.

* Line - 45 - AUC is not defined. Also, the outcomes need to be specified in the abstract (i.e. was area under the curve, incremental area under the curve, or both extracted for data analysis). PPG/PPI are not outcomes. We use AUC/iAUC glucose/insulin to understand PPG/PPI, just like we use HbA1c to understand glycemic control.
This is now added and changed in the abstract.

Methods
* Search was conducted over 1 year ago. Please update.
We have now updated the search until September 2019. This updated yielded 917 titles, of which 24 were screened full-text and 2 were included in the systematic review and meta-analysis. This is now revised throughout the methods and the results of the paper.

* Line 135-136 - it is inappropriate to pool data with AUC and iAUC, as they occasionally produce different results depending on the baseline value.
We admit that this is a confusing sentence, as this line refers to the data as extracted. We have now checked this again in all included studies and all data were used in iAUC. So, the exposure was calculated as a %change in iAUC. We have simplified the sentence now in the manuscript.

* Line 139-141 - What was extracted as the main endpoint(s) for the data analysis? Was it mean difference (MD)? Or relative changes? This needs to be specified in the methods.
Agree, this should be clarified. We have added this to the methods section on page 7 line 148 as follows: 'The outcome was a mean difference between intervention and control'.

Results
* Serious methodological limitation: some acute and chronic trials within a study were conducted in different populations (Asai et al., Kallio et al., McMillan-Price et al., Nakayama et al., Shimabukuro et al., 2013). Some may argue that this equivalent to a treatment type being studied by two different authors (i.e. same treatment (x), author 1 studies x in acute setting; author 2 studies x in long-term setting. If this is the case, there may be quite a few
trial comparisons that may have been missed that could answer the main study question.

For example, several comparisons may be extracted from the following meta-analyses:

- Evans et al. 2017, Fructose replacement of glucose or sucrose in food or beverages lowers postprandial glucose and insulin without raising triglycerides: a systematic review and meta-analysis, AJCN
- Evans et al. 2017, Chronic fructose substitution for glucose or sucrose in food or beverages has little effect on fasting blood glucose, insulin, or triglycerides: a systematic review and meta-analysis, AJCN

We do not agree with the suggestion of the reviewer that studies of similar treatments by different authors (investigator groups, labs) could have been included in the present review. The differences between ‘authors’ will inevitably involve differences in meal composition (caused by sources and availability of foods, preparation methods), as well as study protocol, including laboratory measurements. We have extrapolated acute effects from different populations only in cases where authors themselves referred to the acute study and described this as the same intervention type. In addition, we checked the references kindly provided by the reviewer. The reason not to include these in the present study is that the acute and chronic exposures were not investigated by the same authors or in the same groups of individuals, which was an important part of the remit for this meta-analysis, as previously mentioned. In addition, we updated our systematic review until September 2019 and this yielded 1 additional study on acute effects that was combined with an already identified study. We now included this pair of studies in our review and meta-analysis and updated this throughout the paper.

The duration of the acute studies was different (i.e. 180 mins, 240 mins) among studies which could produce larger AUCs by nature of design (even if they are crossover studies). How were these adjusted for? This could also possibly add to the heterogeneity. Ratio of means could be a possible alternative.

The reviewer is correct that duration of responses differed between studies. We have adjusted for this by using the difference in iAUC as a % of the control iAUC. One could argue that larger differences can potentially be seen with shorter measurement duration, as the largest potential reductions in postprandial response may be apparent in the early phase of the postprandial response. However, this is all speculative and probably dependent on the type of intervention. The ratio is an interesting concept and carefully considered the papers provided below. However, the ratio does not provide advantage over a percentage in ruling out the heterogeneity caused by different durations. Moreover, using a ratio complicates the interpretation of the results. We therefore did not use a ratio to present our results.

- Friedrich et al. 2008, The ratio of means method as an alternative to mean differences for analyzing continuous outcome variables in meta-analysis: a simulation study. BMC Med Res Methodol.
- Friedrich et al. 2011, Ratio of means for analyzing continuous outcomes in meta-analysis performed as well as mean difference methods. J Clin Epidemiol.

MINOR COMMENTS

Abstract

* Line 34 - "the relationship of acute glucose *and* insulin postprandial responses…"
  Done.

* Line 39 - postprandial glucose (PPG) *and/or*
  Done

* Line 46 - units for MD are not correct. Shouldn't they be mmol*min/L and pmol*min/L?
  The units are correct since the MD of postprandial responses was given as a AUC (unit mmol*h/L) corrected for time (divided by h), which implies that units are mmol/l and pmol/l. The time correction was needed for standardized analyses of MD in PPG. The interpretation of the MD is the difference in average PP level (averaged over time of the postprandial period). The reviewer is correct that this is confusing, we changed AUC in ‘mean PPG’, and
explained this method in the data analysis section on page 7 line 165-166: ‘In these additional analyses, the postprandial exposures were expressed as mean postprandial levels, calculated as iAUC divided by time’.

Introduction
* Line 60 - redundant sentence. How about, "Obesity and type 2 diabetes (T2D) are major global concerns"?
Done
* Line 62-63 - "Postprandial *hyper*glycemia, *hyper*insulinemia, and *hyper*lipidemia, have been..."
Done.
* Line 64 - "Moreover, *elevated fasting and postprandial glucose levels are* …"
Done.
* Line 68 - glucose regulation, as measure by what?
This phrasing was unclear and replaced by: 'Indeed, in non-diabetic hyperglycaemia lifestyle treatment or medication to improve glycaemic control was associated with a reduced risk of future diabetes' on page 3 line 72-73.
* Line 76 - "has *not* been *quantified*"
Done.

Methods
* For Supplementary file 1, create a table and include each search term(s) as a row to make it easier to read
Done.
* Line 101 - "by two reviewers". Please indicate who they were.
Done, this is now included on page 5 line 104-106.
* Line 102 - 103 - "Individuals *with prediabetes, type 1 and type 2 diabetes mellitus*;…"
Done
* Line 153 - Why 0.8? Why not 0.5? Please indicate rationale.
We used a correlation of 0.8 to calculate the variance for cross-over studies. Based on previous studies, we assumed a correlation of 0.8 between two measurements within one subject. Since it is a correlation between measurements within one subject, 0.5 is probably too low.

Results
* Line 195 - Table 1
  o For column, "Effect measure" -->
  ✧ please indicate AUC/iAUC glucose/insulin instead of PPG/PPI. PPG/PPI are not the outcomes. We use AUC/iAUC to understand PPG/PPI, just like we use HbA1c to understand glycemic control.
  Done.
  ✧ For "insulin", please specify whether it is "fasting insulin" or "random insulin"
  Done.
* Line 210-211 - please specify direction of change as well
The direction of the change is specified by the minus sign.

* Line 212 - again, absolute PPG is not an outcome. Please indicate whether the MD represents pooled AUC, iAUC, or both.
Mean difference represents the mean postprandial glucose level (calculated ad iAUC/time). PPG was changed to 'mean PPG level'.

* Line 212 - 217 - please specify correct units for MDs.
mean PPI level, in mmol/l for glucose and pmol/l for insulin. This was added.

Supplementary File
Elevated glucose levels in the postprandial state are a key feature of impaired glucose tolerance and diabetes and are a risk marker for cardiovascular diseases. However, despite considerable literature supporting the potential health benefits of reducing postprandial glucose (PPG), and insulin (PPI) exposures, the size of a clinically relevant PPG and PPI reduction is currently unknown. We performed a systematic review and meta-analysis of dietary intervention studies to quantify the relationship of acute glucose or insulin postprandial responses with longer-term effects on diabetes-related risk factors. We searched EMBASE and MEDLINE for dietary intervention studies aiming to reduce postprandial glycaemia, with actual measures of PPG or PPI as acute exposures as well as markers of glucose metabolism and insulin sensitivity after at least 4 weeks of diet intervention as outcomes.

Only a limited number of postprandial glucose lowering dietary intervention studies measured acute postprandial exposures to PPG/PPI during the interventions. The present meta-analyses include 12 publications and provide quantitative estimates of effects of dietary interventions on PPG and PPI responses. In this small heterogeneous set of studies, no associations were found between acute postprandial responses and changes in longer-term diabetes-related risk factors. As conclusion, we recommend that, to enable setting quantitative benchmarks for PPG/PPI reductions, future dietary intervention studies should consider measuring PPG/PPI exposure to study diets before embarking on a long-term dietary intervention. Similarly, investigators should move beyond the single acute meal study and to follow-these up with a chronic intervention, in order to establish the true effects on metabolic risk.

We look forward to hearing from you soon.

Best regards,

Matthieu Flourakis (on behalf of all authors).
ILSI Europe
Reducing postprandial glucose in dietary intervention studies and the magnitude of the effect on diabetes-related risk factors: a systematic review and meta-analysis

Short running head: Postprandial glucose and diabetes risk factors

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**ABSTRACT**

**Purpose**: Reducing postprandial hyperglycemia has beneficial effects on diabetes-related risk factors, but the magnitude of the reduction needed to achieve such an effect is unknown. To quantify the relationship of acute glucose and insulin postprandial responses with longer-term effects on diabetes-related risk factors by performing a systematic review and meta-analysis of dietary intervention studies.

**Methods**: We systematically searched EMBASE and MEDLINE. Dietary intervention studies among any human population aiming to reduce postprandial glycaemia, with actual measures of postprandial glucose (PPG) and/or insulin (PPI) as acute exposures (incremental area under the curve, iAUC) as well as markers of glucose metabolism (fasting glucose, HbA1c) and insulin sensitivity (fasting insulin, HOMA-IR) after at least 4 weeks of diet intervention as outcomes, were included. Meta-analyses were performed for the effects on acute exposures and on diabetes-related risk factors. The relationship between changes in acute exposures and changes in risk factor outcomes was estimated by meta-regression analyses.

**Results**: Out of the 13004 screened papers, 14 papers with 14 comparisons were included in the quantitative analysis. The dietary interventions acutely reduced mean PPG (mean difference (MD), -0.27 mmol/l; 95% CI, -0.41 to -0.14) but not mean PPI (MD, -7.47 pmol/l; 95% CI, -16.79 to 1.86). No significant overall effects on fasting glucose and insulin. HbA1c was reduced by -0.20% (95%CI -0.35 to -0.05). Changes in acute PPG were significantly associated with changes in fasting plasma glucose (FPG) (per 10% change in PPG: β = 0.085 (95% CI, 0.003, 0.167), k=14), but not with fasting insulin (β = 1.20 (95% CI, -0.32, 2.71), k=12). Changes in acute PPI were not associated with changes in FPG (per 10% change in PPI: β = -0.017 (95% CI, -0.056, 0.022), k=11).

**Conclusions**: Only a limited number of postprandial glucose lowering dietary intervention studies measured acute postprandial exposures to PPG/PPI during the interventions. In this small heterogeneous set of studies, an association was found between the magnitude of the acute postprandial responses and the change in fasting glucose but no other outcomes.
More studies are needed to quantify the relationship between acute postprandial changes and long-term effects on risk factors.

Keywords: glucose, insulin, glycemic index, glycemic load, HbA1c

INTRODUCTION

Obesity and type 2 diabetes (T2D) are major global concerns. Recent estimates of T2D expect dramatic increases by 2035 to reach 471 million of cases globally [1]. Postprandial hyperglycemia, as well as the related phenomena of hyperinsulinemia and hyperlipemia, have been implicated in the etiology of chronic metabolic diseases such as T2D [2].

Moreover, elevated fasting and postprandial glucose levels are consistently associated with an increased risk of cardiovascular events, even in the non-diabetic range [3]. To prevent diabetes, an integrated approach is required which includes both dietary modification and regular physical activity [4-6]. Indeed, in non-diabetic hyperglycaemia lifestyle treatment or medication to improve glycaemic control was associated with a reduced risk of future diabetes [7].

A number of papers have hypothesized the value of consuming low glycemic index foods to decrease the overall glycemic response of the diet for long-term benefit. Meta-analyses of the effect of low glycemic index (GI) diets indeed demonstrated beneficial effects on body weight in people with obesity and prevention of T2D and cardiovascular diseases [8-10].

However, the magnitude of the reduction of postprandial glycemic response using dietary interventions such as low GI foods or meals, compared to high GI interventions in relation to longer-term established diabetes-related risk factors has not been quantified. At the moment, the majority of dietary studies investigate individual foods and their ability to reduce glucose levels over a period of a single meal only. It is therefore important to understand the relevance of these single meal studies by investigating the quantitative reductions in PPG/PPI needed acutely to induce relevant changes on established longer-term risk factors chronically, and disease prevention ultimately. Therefore, the aim of this work was to quantify
the relationship between acute glucose and insulin postprandial responses and their effects on diabetes-related risk factors over time by performing a systematic review and meta-analysis of controlled postprandial glucose-lowering dietary intervention studies.
METHODS

Data source and searches
The bibliographic databases Elsevier Medical Database (EMBASE) and the US National Library of Medicine database (MEDLINE via the PubMed portal) were systematically searched for relevant papers until September 13, 2019. Relevant papers that were identified while developing the search string or based on authors' own files were manually included when needed. Search terms were defined by the research question, including terms for GI/glycemic load (GL) dietary interventions, postprandial responses, and study design. Indexed terms were used from MeSH in PubMed and from EMtree in EMBASE. Free-text terms were used in both databases as well. The full search strategies for both databases can be found in Supplementary file 1. The protocol and search strategies used were registered at PROSPERO prior to the study being executed (CRD42018093153).

Study selection
Titles and abstracts were screened in duplicate, independently by pairs of reviewers (MA, JWB, JMD, LE, CR, FS, SV, MDR) and differences were resolved by consensus. Full-text papers were screened independently by two reviewers (MA, JWB, LE, MDR, CR) for eligibility. Studies were included if they: (I) studied any human population, including healthy individuals and individuals with prediabetes, type 1 and type 2 diabetes mellitus; (II) involved any dietary intervention that aimed at reducing GI, GL, or postprandial glucose responses; (III) reported measures of postprandial glucose (PPG) or postprandial insulin (PPI) as acute exposures to study diets; (IV) reported measures of glycemic control and/or insulin sensitivity over time as outcomes. Studies were excluded if they: (I) had a study duration < 4 weeks; (II) were not written in the English language; (III) had no control group; (IV) had co-interventions; (V) had changes in glucose-lowering medication use during study; (VI) had no accessible full-text. If eligible full text papers did not report acute PPG and PPI response data, papers were checked for references to related papers that had previously published this data.
Multiple arms of the same study were included when these arms were independent (had different control groups) [11].

**Data extraction**

Data extraction of the included studies was performed by one reviewer (CR) and was appraised (for a random subsample) by a second reviewer (MA). Information on study design, population, intervention diet, acute PPG and PPI exposures (levels per time point, AUC, incremental AUC (iAUC) and outcome measures (markers of glycemic control and insulin sensitivity) were extracted. In case of missing data on exposures and outcomes, authors were contacted to provide the required information. If authors did not respond and relevant information was available in figures (i.e. bars for AUC, and responses per time point from graphs), data were extracted from figures using the Microsoft Excel add-in tool TM Image-to-data (tushar-mehta.com).

**Quality assessment**

Two reviewers (CR and MA) independently assessed the methodological quality of full-text papers using the Cochrane Risk of Bias Tool [12]. Differences in scores were resolved by consensus. Potential risk of bias was assessed by scoring 7 different items (random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, other sources of bias) with low, high or unclear risk of bias and is presented in Supplementary Figure 1.

**Data synthesis and analysis**

Outcome data were extracted if reported for at least five comparisons. The exposure and outcome measures glucose and insulin, with variance measure were transformed into SI units (mmol/l for glucose (=0.0555*mg/dl) and pmol/l for insulin (=6*microU/ml)).
In case postprandial responses were reported as data per time point (in table or as a figure), iAUC’s were calculated by the trapezoidal method as net iAUC [13]. Relative changes in exposures PPG and PPI were calculated as

$$\frac{iAUC_{\text{intervention}} - iAUC_{\text{control}}}{iAUC_{\text{control}}} \times 100\%.$$  

The outcome was a mean difference between intervention and control. Baseline and post-intervention means with standard deviations (SD) or standard error of the mean (SEM) for the intervention and control groups were extracted, transforming SD into SEM (SEM=SD/√N, where N = subject population). When actual P-values were reported, these were used to estimate the SEM [11]. In parallel studies, the absolute change in outcomes was calculated by subtracting the change from baseline in the control group from the change from baseline in the intervention group. In crossover studies, the post-intervention measure of the control group was subtracted from the post-intervention measure of the intervention group. The variance of the absolute changes in outcomes was calculated as $(\sqrt{SE_{\text{intervention}}^2 + SE_{\text{control}}^2})$ for parallel studies and

$$\left(\sqrt{SE_{\text{intervention \; end}}^2 + SE_{\text{control \; end}}^2 - 2r \times SE_{\text{intervention \; end}} \times SE_{\text{control \; end}}}\right)$$  

for crossover studies, assuming a within-subject correlation coefficient of 0.8.

Random effects meta-regression analyses were conducted (if number of comparisons k > 10) to estimate the association between changes in the acute PPG/PPI exposures and changes in longer-term risk factor outcomes. As additional analyses, overall effects on the acute postprandial exposures and on the outcome variables were estimated by meta-analyses and illustrated by forest plots. In these additional analyses, the postprandial exposures were expressed as mean postprandial levels, calculated as iAUC divided by time.

The Q test (Chi² statistic, P<0.05) was used to evaluate between-study heterogeneity in meta-analysis and the residual heterogeneity in meta-regression analysis. The I² statistic was used for quantification of the degree of heterogeneity and is interpretable as the percentage
of the total association that may be due to heterogeneity between studies ($I^2 > 50\%$ was considered a meaningful level of heterogeneity) in meta-analysis and as the residual heterogeneity in meta-regression analysis after correction for the changes in acute PPG/PPI exposures. The Pearson correlation coefficient between the change in PPG and the change in PPI was calculated. Bubble charts were created to visualize the relationship between the % relative change in PPG/PPI and the change in diabetes-related risk factors. Planned subgroup analyses stratified by normal versus abnormal glucose metabolism (non-diabetic hyperglycemia or diabetes) could not be conducted (because of k comparisons $\leq 10$ per subgroup). Instead, for each comparison, normal versus abnormal glucose metabolism was marked by color in the bubble charts (abnormal glucose metabolism was defined on a study group level, as being either impaired fasting glucose and/or impaired glucose tolerance and/or HbA$_{1c}$ $> 5.7$ (%) and/or use of glucose-lowering medication).

Meta-analysis was conducted in Review Manager (RevMan version 5.3. Copenhagen): The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Meta-regression analysis was performed in R version 3.4.2 using the Metafor package.
RESULTS

The search retrieved 13,004 papers and an additional 3 potentially relevant papers were found manually and added to the database for screening (Figure 1). After removal of duplicates, 6,964 papers were screened based on titles and abstracts; 146 full-text papers were finally assessed for eligibility. Main reasons for exclusion were: acute effects not reported (58 out of 128 excluded papers), not a PPG-lowering dietary intervention, and not a controlled trial. A total of 18 papers were eligible, of which 14 papers delivered all relevant data needed for quantitative analyses [14-25]. Three studies reported acute and chronic effects of the same dietary intervention in different papers [18,26,27] and [22,28,29]. One paper [21] reported data from two intervention and two control diets, thereby adding two independent comparisons. The total number of comparisons retrieved from the included set of papers for the quantitative analyses was 14. For PPG, there were 14 comparisons with outcome FPG, 12 with fasting insulin, and 7 with HbA1c. For PPI, there were 11 comparisons with outcome FPG, 10 for fasting insulin, and 4 for HbA1c. Table 1 summarizes the characteristics of the studies included in the quantitative analyses.

Two out of 14 comparisons aimed to reduce postprandial glucose via mulberry leaf extract supplementation [14,19] while the other comparisons were dietary interventions of whole diet low GI (LGI) versus high GI (HGI) (6 comparisons), low GI breakfast (1 comparison), carbohydrate-reduced high-protein diet (1 comparison), type of rice (2 comparisons) and liquid carbohydrate-modified supplement (2 comparisons). At baseline, five comparisons (four studies) included individuals with normal glucose metabolism and nine comparisons included individuals with abnormal glucose metabolism. The study duration ranged from four weeks to three months. The intervention was applied to ≥ 3 main meals in nine comparisons, and to < 3 main meals in five comparisons. The duration of postprandial measurement ranged from 120 to 540 minutes, with a median and most frequent duration of 180 minutes. The majority of the studies scored a high risk of bias on blinding of participants and personnel (Supplementary Figure 1). All studies scored a low risk of bias on blinding of
outcome assessment and selective reporting. Randomization and allocation concealment scored most frequently an unclear risk of bias.

The acute relative change in iAUC glucose ranged from -121% to 3.5%, with a median of -27.1%. The acute relative change in iAUC insulin ranged from -36.8% to 33.2%, with a median of -29.2%. The correlation between the change in iAUC glucose and the change in iAUC insulin was 0.69 (P = 0.019), see Supplementary Figure 2.

Overall, the dietary interventions acutely reduced absolute mean PPG levels (mean difference -0.27 mmol/l; 95% CI, -0.41 to -0.14; P <0.0001; Supplementary Figure 3A) but this effect was not significant for mean PPI level (mean difference -7.47 pmol/l; 95% CI, -16.79 to 1.86; P = 0.12; Supplementary Figure 3B).

No significant overall chronic effects were found for dietary intervention studies on fasting plasma glucose (mean difference 0.03 mmol/l; 95% CI, -0.27 to 0.33; P = 0.83) and fasting insulin (mean difference 3.10 pmol/l; 95% CI, -2.37 to 8.56; P = 0.27), but an overall reduction in HbA1c was observed (mean difference -0.20%; 95% CI, -0.35 to -0.05; P = 0.01) (Supplementary Figure 4 A-C).

The relationships between % relative acute changes in PPG/PPI and changes in FPG, fasting insulin, and HbA1c are presented in Figure 2 and Supplementary Figure 5. Three out of these six relationships had sufficient comparisons/data (k > 10) to conduct meta-regression analyses (Figure 2). Changes in acute PPG responses were associated with changes in FPG (per 10% change in PPG: β = 0.085; 95% CI, 0.003, 0.167; k=14), but not with fasting insulin (β = 1.196; 95% CI, -0.321, 2.714; k=12). Changes in acute PPI responses were not associated with changes in FPG (per 10% change in PPI: β = -0.017; 95% CI, -0.056, 0.022; k=11). By visual inspection, no differences in results were observed between studies with individuals with normal glucose metabolism versus studies with individuals with abnormal glucose metabolism (Figure 2). Heterogeneity of all meta-analyses and meta-regression results was always below an I² of 50% with the exception of the overall effects of the interventions on FPG (96%) and the association between acute PPG response and FPG (91.4%).
DISCUSSION

This systematic review and meta-analysis of controlled dietary intervention studies aimed to investigate the size of the association between acute PPG and PPI responses and longer-term effects on diabetes-related risk factors. The evidence to examine this association was found to be limited to a set of 13 heterogeneous studies reporting 14 comparisons. An association was found between the size of the reduction in acute PPG exposures to study diets and FPG, but not between PPG and fasting insulin and HbA1c. No associations were found between acute PPI exposures and any of the outcomes.

A strength of this meta-analysis was the systematic approach to identify studies. Moreover, among included studies, the range in both PPG changes (-121% to +4%), and PPI changes (-37% to +33%) was substantial, which provided enough variation in exposures to potentially identify an association with outcomes. An important limitation was that our systematic review procedure yielded only a small number of studies that actually assessed PPG and PPI exposures to the diets under study. Most studies that aimed to reduce such exposures have designed the study diets based on published GI tables, or assumed effects on PPG, without quantification of actual PPG exposures, and were therefore not eligible for the present review. This perhaps identifies a limitation in the way nutritional research is currently undertaken. The small number of studies reduced study power and precluded analyses of effects on other outcomes (HbA1c). Another limitation of this meta-analysis is that the set of included studies were heterogeneous in study design and the number of studies did not allow for stratification by these sources of heterogeneity. Some major sources of potential heterogeneity were glucose metabolism status and the intensity of the intervention. Indeed, subjects with normal and abnormal glucose metabolism might respond differently to low GI interventions with a greater change in FPG reported previously in subjects with poor glycemic control [9]. Intensity of the intervention varied as some involved all meals (whole diet approach) and others one meal only, which hampers quantification of PPG exposures.
during the day. Other potential sources of heterogeneity were study quality, duration of the chronic intervention and compliance to diets. In our selected set of studies, a significant reduction in HbA1c but no other longer-term risk factors (fasting glucose and insulin) following PPG-lowering dietary interventions of at least 4 weeks was found. These findings seem to be somewhat at odds with previous GI/GL epidemiologic and some intervention studies. Indeed, several prospective cohort studies have shown an association between GI/GL and the risk of T2D [30-33]. In a meta-analysis of prospective cohort studies, Barclay et al. concluded on an independent effect of GI/GL on the risk of developing T2D [34]. However, due to their observational nature one cannot exclude the role of confounders (e.g. other dietary factors) in the observed association with T2D. As reviewed by Blaak et al., results from short-term GI/GL intervention on insulin sensitivity and/or secretion still remain inconclusive [2]. While 11 studies demonstrated a beneficial effect on insulin sensitivity or insulin secretion, 10 papers did not report any difference. Livesey et al. performed a systematic review and meta-analysis of intervention trials on GI and markers of health [9]. They concluded on a favorable effect of consumption of reduced glycemic response diets on reduction of FPG and glycated proteins. However, the effect of low GI interventions seems to vary according to the subjects' glucose control status. Indeed, the improvement in fasting blood glucose and glycated proteins was reported to be greater in subjects with poor fasting glucose control (> 5 mmol/L). Also, weak evidence suggested a reduction in fasting insulin concentration, only in people with overweight or obesity with fasting insulin concentrations above 100 pmol/L. We did not have sufficient data to tease out differential effects between individuals with normal versus abnormal glucose metabolism, but the visual inspection did not indicate any differences between studies among individuals with normal versus abnormal glucose metabolism. The discrepancies with Livesey's meta-analysis may be partially explained by the studies included [9]. Indeed, we only included studies in which the effect on the acute reductions of postprandial glycemia was quantified, while this effect was not assessed in most of the 45 publications included in Livesey et al's meta-analysis [9]. Despite the lack of overall effect on fasting glucose, the present study
revealed a relationship of PPG with fasting plasma glucose. Given the heterogeneity of the studies and the lack of overall effect on fasting glucose, these results should be interpreted with care. On the other hand, our data do provide some support for a relationship between the size of the postprandial glucose response and the size of the reduction in fasting glucose.

Although there is abundant evidence that elevated blood glucose, concomitantly with elevated insulin concentration, leads to a transitory deleterious metabolic and hormonal state and oxidative stress, involving the liver, the pancreas, skeletal muscles, lipid metabolism interactions as well as incretins and inflammatory parameters, the exact role of PPG and the relevant magnitude of effect in this process remains unknown [2]. However, it has been postulated that glycemic variability may be a much better indicator for related metabolic effects [35]. Indeed, multiple cohort studies have shown that a high glycemic variability is associated with an increased risk of cardiovascular disease in people with T2D independent from mean plasma glucose or HbA1c [36-38].

Daily exposures to glucose can currently be measured relatively non-invasively via Continuous Glucose Monitoring (CGM) systems. In the present dataset, only one of the included studies utilized this system [28]. In an observational study that used CGM, a positive relationship between PPG and HbA1c was found, both in healthy individuals and those with diabetes [39]. Further application of CGM in (dietary) intervention studies that aim to reduce glycemic exposure would provide better understanding of achieved reductions in overall PPG exposure and variability. This will enable the estimation of relevant PPG reductions as well as setting benchmarks for PPG exposure in future interventions.

In conclusion, only a limited number of postprandial glucose lowering dietary intervention studies measure the actual reductions in acute PPG/PPI to the intervention which they then go on to administer chronically. In this small heterogeneous set of studies, an association was found between the magnitude of the acute postprandial responses and the change in fasting glucose but no other outcomes. To enable setting quantitative benchmarks for PPG/PPI reductions, future dietary intervention studies should consider measuring PPG/PPI
exposure to study diets before embarking on a long-term dietary intervention. Similarly, investigators should be encouraged to move beyond the single acute meal study and to follow these up with a chronic intervention, in order to establish the true effects on metabolic risk.
Abbreviations list:

BR, brown rice; CGM, continuous glucose monitoring; CHO, carbohydrate; DNJ, deoxynojirimycin; E, energy; F, females; FPG, fasting plasma glucose; GBR, glutinous brown rice; GI, glycemic index; GL, glycemic load; HGI, high glycemic index; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; iAUC, incremental area-under-the-curve; LGI, low glycemic index; M, males; MD, mean difference; MLAE, mulberry leaf aqueous extract; ONS, oral nutritional supplement; PPG, postprandial glucose; PPI, postprandial insulin; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis; QUICKI, Quantitative Insulin Sensitivity Check Index; SD, standard deviation; SEM, standard error of the mean; T2D, type 2 diabetes; WR, white rice
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Conflict of Interest:

At the time of conducting the study, MA was employee of Unilever, a manufacturer of consumer food products and LE was employee of Nestec SA; and SV is employee of Mondēlez International R&D; CR, EEB, PD, FS, JWB, JMD, PD, and MDR have nothing to disclose. We thank Linda Schoonmade from VU University Amsterdam for designing and executing the literature search strategy. We also thank Femke Sijtsma and Jacqueline M Dekker for their contribution.
Author's contribution

MA, EEB, LE, PD, SV and MDR: Designed research (project conception, development of overall research plan, and study oversight): CR, MA, EEB, LE, PD, FS, SV, MDR: conducted research (hands-on conduct of the experiments and data collection) CR, MA, FS: analyzed data or performed statistical analysis and analyzed the extracted data; CR, MA, EEB, LE, SV, JWB, MDR wrote the manuscript; CR, MA and JWB had responsibility for final content, all authors edited and commented a version of the manuscript.
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**Figure 1.** PRISMA flow chart of study inclusion.

PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis

GI, glycemic index; GL, glycemic load.

**Figure 2.** Bubble charts of the relationship between % relative change in PPG and absolute change in (a) FPG (b) fasting insulin. (c) The relationship between % relative change in PPI and absolute change in FPG. The size of the bubbles indicates the weight of each study (inverse variance). \(^a\) per 10% change in PPG. \(^b\) per 10% change in PPI.

Random effects meta-regression analyses were conducted (if number of comparisons \(k > 10\)) to estimate the association between changes in the acute PPG/PPI exposures and changes in longer-term risk factor outcomes. The \(I^2\) statistic was used for quantification of the degree of heterogeneity and is interpretable as the percentage of the total association that may be due to heterogeneity between studies (\(I^2 > 50\%\) was considered a meaningful level of heterogeneity) in meta-analysis and as the residual heterogeneity in meta-regression analysis after correction for the changes in acute PPG/PPI exposures. Bubble charts were created to visualize the relationship between the % relative change in PPG/PPI and the change in diabetes-related risk factors. For each comparison, normal versus abnormal glucose metabolism was marked by color in the bubble charts (abnormal glucose metabolism was defined on a study group level, as being either impaired fasting glucose and/or impaired glucose tolerance and/or \(\text{HbA}_{1c} > 5.7\%\) and/or use of glucose-lowering medication). Meta-regression analysis was performed in R version 3.4.2 using the Metafor package.

FPG, fasting plasma glucose; PPG, postprandial glucose; PPI, postprandial insulin.
Records identified through database searching Embase (n = 7377) and Pubmed (n = 5627) (n = 13004)

Additional records identified through other sources (n = 3)

Records after duplicates removed (n = 6964)

Records screened (n = 6964)

Records excluded (n = 6818)

Full-text articles assessed for eligibility (n = 146)

Studies included in qualitative synthesis (n = 18)

Studies included in quantitative synthesis (meta-analysis) (n = 14)

Full-text articles excluded, with reasons (n = 128):
- No acute effects reported (n = 58)
- Not GI/GL intervention (n = 29)
- Wrong study design (n = 25)
- Study duration < 4 weeks (n = 4)
- Not English language (n = 4)
- No chronic effects reported (n = 3)
- Co-intervention (n = 2)
- Full-text not accessible (n = 2)
- Changes in glucose-lowering medication use during the intervention study (n = 1)

For more information, visit www.prisma-statement.org.
Figure 2. Bubble charts of the relationship between % relative change in PPG and absolute change in (A) fasting plasma glucose (FPG); (B) fasting insulin; (C) The relationship between % relative change in PPI and absolute change in FPG. Blue dot: Studies among individuals with normal glucose metabolism. Red dot: studies among individuals with abnormal glucose metabolism. The bubble size reflects the weight of the study in the analysis (inverse variance). a per 10% change in PPG. b per 10% change in PPI.
| Author, Year, Country | Characteristics of participants | Study design | Duration | Intervention | Control | Provision of meals / products | Effect measure |
|-----------------------|---------------------------------|--------------|----------|--------------|---------|-------------------------------|----------------|
| Asai et al., 2011, Japan | 2 F and 8 M subjects with abnormal glucose metabolism (50.0 ± 10.6 years) BMI 24.3 ± 1.7 kg/m² | Randomized crossover | 120 min | Carbohydrate tolerance test – 200 g boiled white rice with 2 g of dry seasoning (311 kcal, 70 g CHO, 4.8 g protein, 1.3 g fat) 15 min after ingestion of a mulberry leaf extract capsule (6 mg DNJ). | Carbohydrate tolerance test with placebo capsule. | | iAUC glucose, iAUC insulin |
| Chronic intervention | 22 F and 43 M subjects with abnormal glucose metabolism (53.6 ± 6.4 years) BMI 24.6 ± 2.5 kg/m² | Randomized parallel | 12 weeks | Diet – applied to three main meals Mulberry leaf extract (6 mg DNJ) capsules were ingested t.i.d. before meals. | Diet – applied to three main meals Placebo capsules were ingested t.i.d. before meals. | The mulberry leaf extract and placebo capsules were provided. | FPG, fasting insulin, HbA₁c |
| Bouche et al., 2002, France | 11 M subjects with normal glucose metabolism (mean 46 ± 9.9 years) BMI 28 ± 3.3 kg/m² | | 240 min | LGI breakfast (38%). The breakfast had the same LGI percent as the diet for the chronic period. | HGI breakfast (75%). The breakfast had the same HGI percent as the diet for the chronic period. | | iAUC glucose, iAUC insulin |
| Chronic intervention | Same as above | Randomized crossover | 5 weeks | Whole diet approach LGI diet: foods with a GI < 45%. | Whole diet approach HGI diet: foods with a GI > 60%. | Special cereals and LGI cookies were provided, otherwise participants were supplied with a | FPG, fasting insulin, HOMA |
| Study                          | Type of Test | Participants                                                                 | Duration | Intervention Details                                                                                                                                                                                                 | Outcomes                                                                                         |
|-------------------------------|--------------|------------------------------------------------------------------------------|----------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|
| Giacco et al., 2014, Italy    | Acute test   | 31 F and 23 M subjects with normal glucose metabolism (57.2 ± 8.3 years) BMI 31.8 ± 5.6 kg/m² | 120 min  | Lunch meal resembling the composition of the recommended diet before start of the intervention. Lunch meal resembling the composition of the recommended diet before start of the intervention. | iAUC glucose, iAUC insulin                                                                       |
| Chronic intervention          | Same as above| Randomized parallel 12 weeks Diet – applied to three main meals Whole-grain cereal products diet. |          | Diet – applied to three main meals Refined cereal products diet. Cereal products represented 60-80% of the daily CHO intake; the remaining 20-40% were provided by fruits and vegetables. Test products in both diets were provided. | FPG, fasting insulin, HOMA-IR                                                                  |
| Kabir et al., 2002, France    | Acute test   | 13 M subjects with abnormal glucose metabolism (59 ± 7.2 years) BMI 28 ± 3.6 kg/m² | 180 min  | LGI breakfast that was the same as during the intervention period HGI breakfast that was the same as during the intervention period | iAUC glucose, iAUC insulin                                                                       |
| Chronic intervention          | Same as above| Randomized crossover 4 weeks Diet – applied to one main meal LGI breakfast (GI 40%) Diet – applied to one main meal HGI breakfast (GI 64%) |          | Treatment foods for breakfasts were provided during the study | FPG, fasting insulin, HbA₁c                                                                 |
|                               |              |                                                                              |          |                                                                                           |                                                                                                |
|                               |              |                                                                              |          |                                                                                           |                                                                                                |
| Study                          | Test Type          | Subjects                                      | BMI (± SD)  | Duration | Meal Description                                                                 | Participants Description                                                                                       | iAUC Measures          |
|-------------------------------|--------------------|-----------------------------------------------|-------------|----------|--------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------|------------------------|
| Kallio et al. 2007 and        | Acute test         | 9 F and 10 M subjects with metabolic syndrome | 31.9 ± 0.7  | 180 min  | The test meal consisted of oat and wheat breads or rye breads, 40 g cucumber, and 3 dL of a no-calorie orange drink. | Provided test breads and baked products during the study (>25% daily energy intake). Pasta and powdered mashed potatoes were provided. | glucose, insulin       |
| Kallio et al. 2008, Finland   |                    |                                               |             |          | The test meal consisted of rye breads, 40 g cucumber, and 3 dL of a no-calorie orange drink. |                                                                                                               |                        |
|                                | Chronic intervention| 23 F and 24 M subjects with abnormal glucose metabolism | 32.0 ± 2.8  | 12 weeks | Whole diet approach Oat-wheat potato diet                                      | Participants replaced their normal breads and baked products with the test breads provided during the study (>25% daily energy intake). | glucose, insulin       |
|                                |                    |                                               |             |          | Whole diet approach Rye-pasta diet                                             |                                                                                                               |                        |
|                                |                    |                                               |             |          |                                                                                   |                                                                                                               |                        |
|                                |                    |                                               |             |          |                                                                                   |                                                                                                               |                        |
| Kim et al., 2014, Korea        | Acute test         | 23 F and 15 M subjects with abnormal glucose metabolism | 25.3 ± 3.2  | 120 min  | A high-CHO meal in the morning (76 g of white bread and 24 g strawberry jam, 407 kcal, 80 g CHO, 8 g protein, 9.7 g fat) followed within 15 | A high-CHO meal in the morning (76 g of white bread and 24 g strawberry jam, 407 kcal, 80 g CHO, 8 g protein, 9.7 g fat) followed within 15 | glucose, insulin       |
| Study | Design | Population | Intervention | Outcome Measures |
|-------|--------|------------|--------------|------------------|
| Mayr et al., 2016, Germany | Chronic intervention | Same as above | Randomized parallel | 4 weeks | Diets – applied to three main meals<br>Six tablets of standardized MLAE with each meal (18 tablets per day: 5 g MLAE (3.6 mg/g of DNJ)).<br>MLAE tablets or placebo tablets provided. | FPG, fasting insulin |
| Acute test | 20 F and 20 M subjects with abnormal glucose metabolism (83.0 ± 5.8 years) BMI 23.9 ± 4.0 kg/m² | 240 min | 200 ml carbohydrate modified oral nutritional supplement. | iAUC glucose, |
| Chronic intervention | Same as above | Randomized parallel | 12 weeks | Intervention – applied two times daily<br>- 2 x 200 ml/day, in between regular meals, diabetes-specific carbohydrate modified oral nutritional supplement (ONS).<br>Control – applied two times daily<br>Standard oral nutritional supplement (ONS) 2 x 200 ml/day in between regular meals.<br>The study nutritional products (ONS) were provided to the subjects. | FPG, fasting insulin, HbA₁c, HOMA-index |
| McMillan-Price et al., 2006, Australia | Acute test | 11 F subjects (26.5 ± 14.6 years) BMI 30.0 ± 14.3 kg/m² | Randomized crossover | 180 min | Mixed meals representative of each diet were fed over 10-hour period | iAUC glucose, iAUC insulin |
| Chronic intervention | 98 F and 31 M subjects with normal glucose metabolism | Randomized parallel | 12 weeks | Diets – whole diet approach<br>High CHO (55%)<br>Diets – whole diet approach<br>High CHO (55%)<br>All key CHO and protein foods and some preprepared | FPG, fasting insulin,
| Study                        | Design                  | Participants                                                                 | Interventions                                                                 |
|------------------------------|-------------------------|-------------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| Nakayama et al. 2017 and     | Acute test              | 13 F and 17 M subjects with abnormal glucose metabolism (61.1 ± 12.5 years) BMI 26.3 ± 3.9 kg/m² | Breakfast with GBR and side dishes (omelet, hamburger, white fish fillet, or salmon) |
| Terashima et al. 2017, Japan | Chronic intervention    | 4 F and 12 M subjects with abnormal glucose metabolism (64.0 ± 8.8 years) BMI 25.7 ± 5.6 kg/m² | Diets – applied to two main meals Glutinous brown rice twice daily |
| Nazare et al., 2010, France  | Acute test              | 19 F and 19 M subjects with normal glucose metabolism (38.3 ± 9.2 years) BMI 27.3 ± 1.5 kg/m² | Breakfast consisting of plain biscuits (LGI) with exactly the same composition as those ingested during the study. |
|                              | Chronic intervention    | Same as above                                                                 | Breakfast consisting of flakes (HGI) with exactly the same composition as those ingested during the study. |

**Note:**
- **HGI:** High glycaemic index
- **LGI:** Low glycaemic index
- **GBR:** Glutinous brown rice
- **WR:** White rice
- **FPG:** Fasting plasma glucose
- **HbA1c:** Glycated haemoglobin A1c
- **iAUC:** Incremental area under the curve
- **GI:** Glycaemic index
- **HOMA-IR:** Homeostasis model assessment of insulin resistance
- **QUICKI:** QUICKI index

*Example values and conditions provided for illustrative purposes.*
| Study                        | Type               | Participants                                      | Design                              | Duration | Intervention Description                                                                 | Outcome Measures                              |
|------------------------------|--------------------|---------------------------------------------------|--------------------------------------|----------|------------------------------------------------------------------------------------------|-----------------------------------------------|
| Samkani et al. 2018 and Skytte et al., 2019, Denmark | Acute test        | 14 M and 2 F subjects with type 2 diabetes and treated with metformin only (median age 65 (43-70)) BMI 30 ± 4.4 kg/m² | Randomized crossover                  | 450 min  | Carbohydrate-reduced high protein diet (31% carb, 29% protein, 40% fat) breakfast (t=0) and lunch (t=270) | iAUC glucose, iAUC insulin                     |
| Chronic intervention         |                    | 28 M and F subjects with type 2 diabetes          | Randomized crossover                  | 6 weeks  | Carbohydrate-reduced high protein diet (30% carb, 30% protein, 40% fat)                  | FPG, fasting insulin, HbA1c                  |
| Shimabukuro et al., 2013, Japan | Acute test        | 6 M subjects with the metabolic syndrome (41 ± 5 years) BMI 28.1 ± 4.3 kg/m² |                                      | 240 min  | A meal (450 kcal) including BR of Japonica variety (200 kcal)                           | iAUC glucose, iAUC insulin                     |
| Chronic intervention         |                    | 27 M subjects with abnormal glucose metabolism (Age: unknown) BMI 26.7 ± 3.5 kg/m² | Randomized crossover                  | 8 weeks  | Diets – applied to one main meal Brown rice of Japonica variety in a single daily meal | FPG, fasting insulin, HbA1c, HOMA-IR          |
| Stenvers et al., 2014, the Netherlands | Acute test        | 10 F and 10 M subjects with abnormal glucose metabolism (60 ± 7 years) BMI 30.7 ± 6.4 kg/m² |                                      | 180 min  | Low-glycemic response liquid meal (mean of the first 4 days of the intervention period) | iAUC glucose                                  |
| Chronic intervention         |                    | Same as above                                     | Randomized crossover                  | 3 months | Diets – applied to one main meal Low-glycemic response liquid                            | FPG, fasting insulin, HbA1c                  |
breakfast (isoenergetic amount of Glucerna SR) low-glycemic breakfast in the preferred taste.

Abnormal glucose metabolism: impaired fasting glucose and/or impaired glucose tolerance and/or HbA1c > 5.7 (%) and/or use of glucose-lowering medication. BR, brown rice; CHO, carbohydrate; DNJ, deoxynojirimycin; E, energy; F, females; FPG, fasting plasma glucose; GBR, glutinous brown rice; GI, glycemic index; HGI, high glycemic index; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; LGI, low glycemic index; M, males; MLAE, mulberry leaf aqueous extract; ONS, oral nutritional supplement; PPG, postprandial glucose; PPI, postprandial insulin; QUICKI, Quantitative Insulin Sensitivity Check Index; WR, white rice
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