Clinical Nutrition 38 (2019) 2827–2832

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Original article

Title: Differentiating the effects of whey protein and guar gum preloads on postprandial glycemia in type 2 diabetes

Linda E. Watson, Liza K. Phillips, Tongzhi Wu, Michelle J. Bound, Helen Checklin, Jacqueline Grivell, Karen L. Jones, Michael Horowitz, Christopher K. Rayner*

Adelaide Medical School, The University of Adelaide, Adelaide, Australia

ARTICLE INFO

Article history:
Received 25 June 2018
Accepted 10 December 2018

Keywords:
Whey protein
Guar gum
Gastric emptying
Type 2 diabetes
Incretin hormones
Postprandial glycemia

ABSTRACT

Background and aims: Whey protein and guar gum have both been reported to reduce postprandial glycemia in health and type 2 diabetes, associated with stimulation of glucagon-like peptide-1 (GLP-1) and/or slowing of gastric emptying. Our aim was to evaluate, in type 2 diabetes, the acute effects of low dose "preloads" of whey and guar, given alone or in combination before a meal, on postprandial glycemia, insulin, GLP-1, and gastric emptying.

Methods: 21 patients with type 2 diabetes, managed by diet or metformin alone, were each studied on 4 days. They received a preload "shake" 15min before a mashed potato meal (368.5 kcal) labeled with ^{13}C-octanoic-acid. The preloads comprised either (i) 17 g whey (W), (ii) 5 g guar (G), (iii) 17 g whey + 5 g guar (WG) each sweetened with 60 mg sucralose, and (iv) 60 mg sucralose alone (control; C), all dissolved in 150 mL water. Venous blood was sampled frequently for measurements of glucose, insulin, and GLP-1 concentrations. Gastric half-emptying time (T50) was calculated from breath $^{13}CO_2$ excretion over 240 min.

Results: Postprandial blood glucose concentrations were lower with W and WG compared to C (each $P < 0.0001$, treatment × time interaction), and lower after G than C only at 30min. Insulin, GLP-1, and glucagon concentrations were higher after W than WG, G, or C ($P < 0.05$, treatment × time interaction), without differences between the latter three. Gastric emptying was slower with W (T50: 179.6 ± 6.1 min, $P < 0.05$) and WG (T50: 197.6 ± 9.7 min, $P < 0.0001$) when compared to C (T50: 162.9 ± 6.2 min), but did not differ between G (T50: 171.3 ± 7.0) and C ($P > 0.99$).

Conclusion: Both whey and whey/guar preloads reduced postprandial glycemia, associated with slowing of gastric emptying. Low dose guar was less effective as a preload for glucose-lowering and did not slow gastric emptying.

Clinical Trial Registry number and website: Australian and New Zealand Clinical Trials Registry, Trial ID ACTRN12615001272583, http://www.anzctr.org.au

Introduction

There is increasing recognition of the importance of lowering postprandial blood glucose, as opposed to fasting or pre-prandial glycemia, to achieve target HbA1c and reduce glycemic variability and cardiovascular risk in type 2 diabetes [1–3]. Nutritional strategies to reduce postprandial glycemia are attractive, and represent the greatest opportunity for optimising glycemic control at an affordable cost as the healthcare demands of society escalate.

Both the rate of gastric emptying, and the actions of the incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), are major determinants of postprandial glycemic excursions [4,5]. In both health and type 2 diabetes, postprandial glycemia is attenuated by interventions that slow gastric emptying, and exacerbated by those that accelerate it [4,6,7]. In health, GLP-1 and GIP both account for the augmentation in insulin secretion after oral compared to isoglycemic intravenous glucose administration (the "incretin" effect). In type 2 diabetes, the insulinotropic effect of GIP is diminished, whereas GLP-1 retains its capacity to stimulate

* Corresponding author. Adelaide Medical School, The University of Adelaide, Level 5, Adelaide Health and Medical Sciences Building, Cnr North Terrace and George St, Adelaide 5000, Australia.Fax: +61 8 83137794.
E-mail address: chris.rayner@adelaide.edu.au (C.K. Rayner).

https://doi.org/10.1016/j.clnu.2018.12.014
0261-5614/

insulin secretion, and also slows gastric emptying [8,9] and suppresses glucagon secretion and energy intake [10]. Accordingly, stimulation of GLP-1 secretion is appealing in the management of type 2 diabetes.

Our group has developed the concept of giving macronutrient "preloads" such as poorly absorbed carbohydrate [11], or protein [12] at a fixed interval before a meal, so that the presence of nutrients in the small intestine stimulates the release of gut hormones, including GLP-1, augments insulin secretion [12,13], and slows gastric emptying of the meal. We have reported that 55 g whey protein given 30 min before a high carbohydrate meal markedly reduced postprandial blood glucose (by ~3 mmol/L) via these mechanisms in type 2 diabetes [12]. However, such a dose of whey entails a large energy load (210 kcal), and would be relatively expensive if used regularly.

Guar gum is a viscous soluble fibre, and when given with a meal, can decrease postprandial glycaemic excursions by slowing gastric emptying [14] and inhibiting small intestinal absorption of glucose [15,16], associated with reduced, rather than increased plasma insulin levels, as well as attenuation of plasma GLP-1 and GIP. Guar supplementation has also been associated with reductions in waist circumference, HbA1c and serum trans-fatty acids in patients with type 2 diabetes [17]. Accordingly, combining both guar gum and whey protein in a dietary supplement may be advantageous. A low dose of whey (17 g), when combined with 5 g guar and taken 15 min before a high carbohydrate test meal, was recently reported to reduce postprandial blood glucose excursions in type 2 diabetes [18], and has an energy burden of only 90 kcal, making it preferable to higher dose preloads for regular consumption. However, the relative contribution of whey and guar to glucose-lowering and slowing of gastric emptying when used alone, and whether their actions are additive or synergistic when given together, are uncertain.

The aims of this study were to compare directly the acute effects of whey protein and guar gum preloads, either alone or in combination, on postprandial glycemia, insulin, GLP-1, and gastric emptying in type 2 diabetes.

Materials and methods

Subjects

Twenty one patients with type 2 diabetes (16 males, 5 females), managed by diet (n = 9) or a stable dose of metformin (n = 12) only, were studied after providing written, informed consent. Their age (mean ± standard error) was 66 ± 2 years, body mass index (BMI) 30.8 ± 1.0 kg/m^2, HbA1c 6.4 ± 0.1% (46.4 ± 1.5 mmol/mol), and duration of known diabetes 6.3 ± 1.9 years. None had significant comorbidities of diabetes, were smokers, or were taking any medication known to affect gastrointestinal function. The protocol was approved by the Human Research Ethics Committee of the Royal Adelaide Hospital and conducted in accordance with the principles of the Declaration of Helsinki as revised in 2000. The trial was prospectively registered with the Australian New Zealand Clinical Trials Registry (ACTRN12615001272583).

Each patient was studied on 4 occasions, separated by at least 4 days, in a single-blind, randomized, cross-over design. Patients were provided with a standardized evening meal consisting of beef lasagne (McCain Foods, Australia) to be consumed with bread, a non-alcoholic beverage, and one piece of fruit at 1900h on the evening before each study. Subjects were then instructed to abstain from all food and nutrient beverages, but were allowed to drink water until midnight, before attending the laboratory at 0800 h. On arrival, an intravenous cannula was inserted into a forearm vein for repeated blood sampling.

Subjects were given a preload "shake" containing either (i) 17 g whey protein (W), (ii) 5 g high molecular weight guar gum (G) (both provided by Omniblend Innovation, Australia), (iii) 17 g whey protein + 5 g guar gum (WG) each sweetened with 60 mg sucralose, or (iv) 60 mg sucralose alone (control; C). Each preload was dissolved in 150 mL water, and consumed at t = −15 min within 2 min, followed by a standardised semi-solid test meal (t = 0–5 min). The meal consisted of 65 g powdered potato (Deb; Unilever Australia) and 20 g glucose, reconstituted with 200 mL water and one egg yolk containing 100uL ^{13}C-octanoate (368.5 kcal: 61.4 g carbohydrate, 7.4 g protein and 8.9 g fat). Breath samples were collected immediately before, and every 5 min after, meal ingestion for the first hour and every 15 min for a further 3 h for measurement of gastric emptying. Venous blood samples (~15 mL) were taken immediately before administration of the preload (t = −20 min), and at t = 0, 15, 30, 60, 90, 120, 180 and 240 min for measurement of blood glucose, and plasma insulin, total GLP-1 and glucagon. Blood samples were placed in ice-chilled EDTA tubes and were centrifuged at 3200 rpm for 15 min. Plasma was separated and stored at −80 °C for subsequent analysis.

Blood glucose, GLP-1, insulin and glucagon assays

Blood glucose concentrations were measured using a glucometer (Optium Xceed, Abbott Laboratories, USA). Plasma insulin was measured by ELISA immunoassay (10-1113; Mercodia, Sweden), with sensitivity of 1.0mU/L and intra- and inter-assay CVs of 2.7% and 5.8%. Plasma total GLP-1 was measured by radioimmunoassay (GLPIT-36HK; Millipore, USA), with sensitivity of 3 pmol/L, and intra- and inter-assay CVs of 4.8% and 9.7% respectively. Plasma glucagon was measured by radioimmunoassay (GL-32K; Millipore, USA), with sensitivity of 20 pg/mL, and inter- and intra-assay CVs of 13.2% and 3.6%.

Gastric emptying

Gastric emptying of the potato meal, labeled with ^{13}C-octanoic acid, was evaluated by excretion of $^{13}CO_2$ in the breath, measured by non-dispersive infrared spectrometer (FANci2, Fischer ANalysen Instrumente, Germany). The gastric half-emptying time (T50) was calculated using the formula described by Ghoos et al. [19], which has been validated against scintigraphy [20].

Statistical analysis

Data relating to glucose, insulin, GLP-1, and glucagon concentrations were evaluated by 2-way repeated measures analysis of variance (ANOVA) using treatment and time as factors and are shown as mean values ± SEM. Post hoc comparisons, adjusted for multiple comparisons by Bonferroni correction, were performed if ANOVAs revealed significant interactions. Incremental areas under the curves (iAUC) for blood glucose, GLP-1, insulin and glucagon concentrations were calculated using the trapezoidal rule [21]. The iAUCs for glucose, GLP-1, insulin, and glucagon, and the gastric emptying T50, were compared using one-factor ANOVA. Based on our previous studies [12,22], it was determined that inclusion of 21 participants would provide 80% power to detect a 0.6 mmol/l difference between treatments in mean blood glucose concentrations after the test meal, with Bonferroni adjusted $P < 0.05$, to allow for multiple post-hoc comparisons. Relationships between the change in blood glucose from baseline and the T50 were evaluated using the Pearson correlation coefficient. Analyses were performed using GraphPad Prism 7.0 (GraphPad Software, USA). $P < 0.05$ was considered statistically significant.

Results

Blood glucose concentrations

Fasting blood glucose did not differ between the four study days (W 7.4 ± 0.2 mmol/L, G 7.4 ± 0.2 mmol/L, WG 7.6 ± 0.2 mmol/L, C 7.4 ± 0.2 mmol/L). None of the preloads affected blood glucose in advance of the main meal. After the meal, blood glucose concentrations increased on each day before returning to baseline (Fig. 1A). There was a significant treatment effect ($P < 0.05$) and treatment × time interaction ($P < 0.0001$) on postprandial glycemia, such that blood glucose concentrations were lower after W and WG at t = 30, 60, 90 min, and lower after G at t = 30 min only, when compared to C. Blood glucose concentrations were lower after W than WG at t = 120 min, after W than G at t = 60, 90 and 120 min, and after WG than G at t = 60 and 90 min ($P < 0.05$ for each). Blood glucose concentrations were higher after W, G, and WG at t = 180 min when compared to C, without any difference at t = 240 min. Similarly, there was a significant treatment effect on iAUC for blood glucose concentrations ($P < 0.05$), such that iAUC was lower for W than G, and for WG than G ($P < 0.05$ for each) (Table 1). There was no difference in iAUC for G than C ($P > 0.99$).

Plasma insulin concentrations

Fasting plasma insulin concentrations did not differ between the four study days. Plasma insulin increased modestly in advance of the main meal after W, but not WG or G ($P < 0.05$, treatment × time interaction at t = 0 min). After the meal, plasma insulin concentrations increased on each day before returning to baseline (Fig. 1B). There was a significant treatment effect ($P < 0.0001$) and treatment × time interaction ($P < 0.0001$) such that postprandial insulin concentrations were higher after W than C at t = 15, 30 and 60 min, after W than WG at t = 15 and 30 min, and after W than G at t = 15, 30, 60 and 90 min. Postprandial insulin concentrations were lower after G than C at t = 30 and 90 min ($P < 0.05$ for each). There was also a significant treatment effect on the overall iAUC for plasma insulin ($P < 0.05$), such that insulin concentrations were higher after W than G ($P < 0.05$) (Table 1).

Plasma GLP-1 concentrations

Fasting plasma GLP-1 concentrations did not differ between the four study days. Plasma GLP-1 increased in advance of the meal only after W ($P < 0.05$, treatment x time effect, at t = 0 min). After the meal, GLP-1 concentrations increased on each day before returning to baseline (Fig. 1C). There was a significant treatment effect ($P < 0.0001$) and treatment × time interaction ($P < 0.05$), such that postprandial GLP-1 concentrations were higher after W than C from t = 15–180 min, after W than WG from t = 15–120 min, after W than G from t = 15–240 min, and after WG than G at t = 90 and 120 min. Postprandial GLP-1 concentrations were lower after G than C at t = 15 and 60 min ($P < 0.05$ for each). There was a significant treatment effect on the iAUC for plasma GLP-1 ($P < 0.0001$), such that GLP-1 concentrations were higher after W than C, WG and G ($P < 0.05$ for each) (Table 1).

Plasma glucagon concentrations

Fasting plasma glucagon concentrations did not differ between the four study days. Plasma glucagon increased in advance of the main meal after W ($P < 0.0001$, treatment × time interaction, at t = 0 min) and WG ($P < 0.05$, treatment × time interaction, at t = 0 min) when compared to C, with a greater increase after W

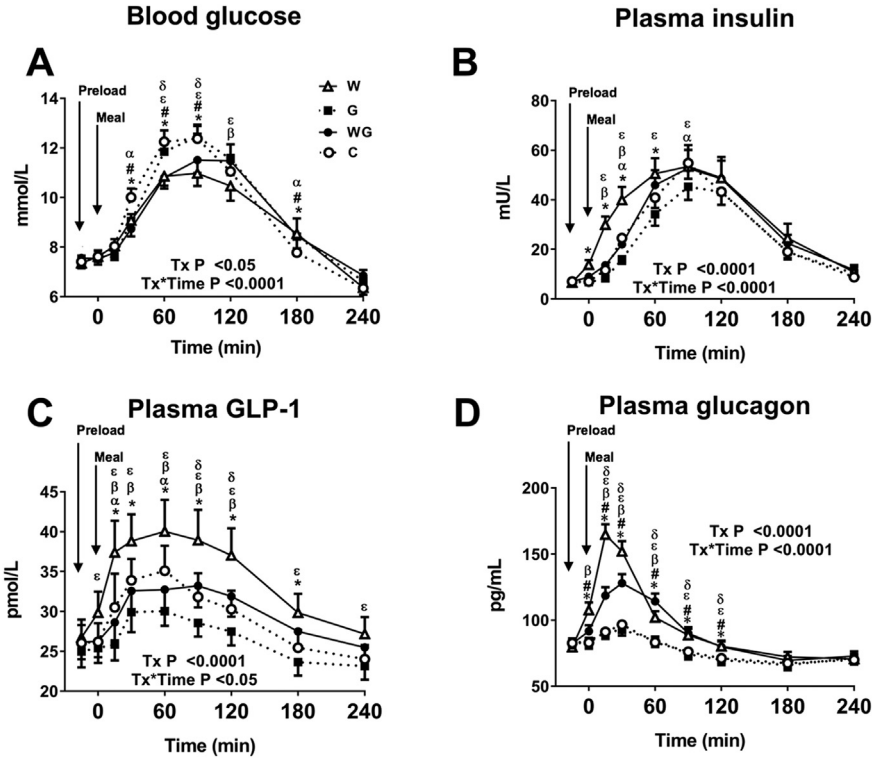

Fig. 1. Effects of preloads whey (W), guar (G), whey/guar (WG), or control (C) on blood glucose (A), plasma insulin (B), plasma GLP-1 (C), and plasma glucagon (D) in response to a high carbohydrate meal in 21 patients with type 2 diabetes. Repeated-measures ANOVA was used to determine statistical difference. Post hoc comparisons were adjusted by Bonferroni-Holm correction. $P < 0.05$ for each treatment × time interaction; *$P < 0.05$ W vs. C, #$P < 0.05$ WG vs C, α$P<0.05$ G vs C, β $P < 0.05$ W vs WG, ε$P<0.05$ W vs G, δ$P<0.05$ WG vs G. Data are mean values ± SEM.

Table 1
Effects of preloads whey (W), guar (G), whey/guar (WG), or control (C) on iAUC, glucose, plasma insulin, plasma GLP-1, and plasma glucagon in response to a high carbohydrate meal in 21 patients with type 2 diabetes.

	C	W	G	WG	*P* value
Glucose iAUC $_{-15-240min}$ (mmol/L·min)	597 ± 53	505 ± 58ε	617 ± 58	506 ± 55δ	<0.05
Insulin iAUC $_{-15-240min}$ (mU/L·min)	5340 ± 629	7041 ± 1139ε	4661 ± 530	5955 ± 833	<0.05
GLP-1 iAUC $_{-15-240min}$ (pmol/L·min)	1180 ± 214	2197 ± 342*β ε	853 ± 183	1256 ± 181	<0.0001
Glucagon iAUC $_{-15-240min}$ (pg/mL·min)	674 ± 107	4663 ± 383*β ε	851 ± 192	3140 ± 335δ#	<0.0001

Data are mean ± SEM. One-factor ANOVA was used to determine statistical difference. Post hoc comparisons were adjusted by Bonferroni-Holm correction. *P < 0.05 W vs. C, β P < 0.05 W vs WG, εP<0.05 W vs G, δP<0.05 WG vs G #*P* < 0.05 WG *vs C*.

than WG (P < 0.05, treatment x time effect, at t = 0 min). After the meal, glucagon concentrations increased on each day before returning to baseline (Fig. 1D). There was a significant treatment (P < 0.0001) and treatment × time interaction (P < 0.0001), such that glucagon concentrations were higher after W than C from t = 15–120 min, after W than WG at t = 15, 30 and 60 min, after W than G from t = 15–120 min, after WG than C from t = 15–120 min, and after WG than G from t = 15–120 min. There was also a significant treatment effect on the overall iAUC for plasma glucagon (P < 0.0001) such that glucagon concentrations were higher after W than C, after W than WG, after W than G, after WG than C, and after WG than G (P < 0.05 for each) (Table 1).

Gastric emptying

There was a treatment effect for gastric emptying (Fig. 2), such that the T50 was greater after WG (197.6 ± 9.7 min) than either C (162.9 ± 6.2 min, P < 0.0001) or G (171.3 ± 7.0, P < 0.05). The T50 was also greater after W (179.6 ± 6.1 min) than C (P < 0.05). While the mean T50 was numerically greater after WG than W, this difference did not achieve statistical significance (P = 0.10). Gastric emptying was similar between G and C (P > 0.99). In a pooled analysis of all subjects on all four study days, there was an inverse relationship between the change in blood glucose between t = 0–60 min and T50 (r = −0.59, P < 0.0001) such that when gastric emptying was slower (i.e. T50 greater), the rise in postprandial glucose was less (Fig. 3).

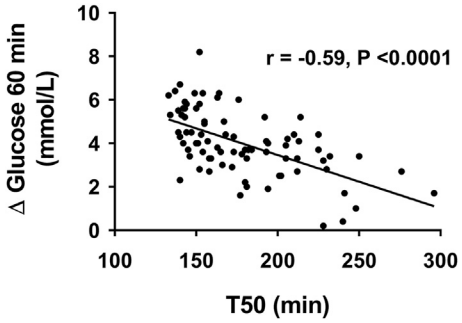

Fig. 3. Relationship between change in blood glucose at 60 min and gastric emptying (T50) evaluated using the Pearson correlation.

Discussion

In patients with type 2 diabetes managed by diet or metformin alone who have relatively good glycemic control, we observed that (i) a low dose whey preload reduced the postprandial glycemic response to a high carbohydrate meal, associated with stimulation of insulin, GLP-1, and glucagon before and after the main meal, and slowing of gastric emptying; (ii) a low-dose guar preload reduced only the early postprandial glycemic response, attenuated postprandial insulin and GLP-1 secretion, and did not slow gastric emptying; and (iii) the combined whey/guar preload exhibited similar effects on postprandial glycemia and gastric emptying to those of whey alone, but was associated with relatively attenuated insulin, GLP-1, and glucagon secretion.

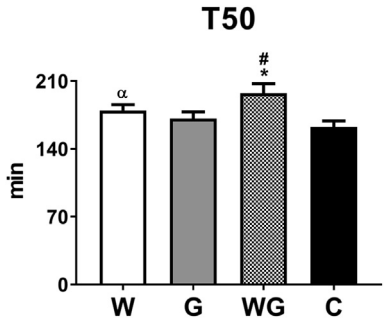

Fig. 2. Effects of preloads whey (W), guar (G), whey/guar (WG), or control (C) on gastric emptying half time (T50) of a high carbohydrate meal in 21 patients with type 2 diabetes. One-factor ANOVA was used to determine statistical difference. Post hoc comparisons were adjusted by Bonferroni-Holm correction. *P < 0.05 W vs C. #P < 0.0001 WG vs. C, αP<0.05 WG vs G. Data are mean values ± SEM.

Whey reduces postprandial glycemia by stimulating the release of GLP-1 and augmenting insulin secretion [12,13] as well as slowing gastric emptying [12], while guar reduces postprandial glycemia through slowing gastric emptying [14] and inhibiting small intestinal absorption of glucose [15,16]. In our study, both the whey and whey/guar preloads were effective in reducing postprandial glycemia and slowing gastric emptying, supporting the use of either as a glucose-lowering therapy. Guar reduced the early rise in blood glucose at the 30 min time point only, and had a neutral effect on gastric emptying whether given alone or when added to whey. This is in contrast to our previous report that showed slowing of gastric emptying when guar was added to a glucose drink [14], although in the latter study the dose of guar used was higher (9 g). The reduction in postprandial glycemia with guar may, therefore, be related to inhibition of intestinal absorption of glucose as opposed to slowing of gastric emptying. It has previously been established, moreover, that guar is much more effective for lowering glycemia when added to a high-carbohydrate meal than when given as a pre-meal drink [23]. When pooling data from all the preloads, however, we observed a strong correlation between the postprandial rise in blood glucose and the rate of gastric emptying, consistent with the concept that slowing of gastric emptying is a key mechanism for reducing postprandial glycemia [4].

Whey protein is a rich source of essential and branched chain amino acids, which are known to have potent insulinotropic [24] and glucagonotropic [25] properties. We did not measure plasma amino acid concentrations, but the observation that whey stimulated greater insulin and glucagon release than the other preloads supports the concept that amino acids are important in stimulating the secretion of these hormones.

Guar is reported to attenuate the rise in plasma GLP-1 to intraduodenal glucose, and whey protein to stimulate GLP-1 [12]. As expected, the whey preload in our study stimulated GLP-1 release prior to the meal, which was not observed with either the guar or control preloads. The addition of guar to the whey preload reduced this effect substantially, likely due to guar reducing the rate of digestion of whey and the exposure of the products of digestion to the distal small intestinal mucosa [16], where the entero-endocrine cells that release GLP-1 are located. This suggests that the timing of preload ingestion in relation to the subsequent meal may be more critical for the whey preload than for the whey/guar combination, since the effects of the former would be optimised when the peak GLP-1 response coincides with the time of meal ingestion. Conversely, the whey/guar combination may prove to be effective even if given with, rather than in advance of, the meal. Moreover, since glucose-lowering by the whey/guar preload does not appear to be dependent on the stimulation of insulin secretion, it may represent an advantage when given to patients with type 2 diabetes who have substantial beta cell dysfunction. However, we acknowledge that we would need specifically to evaluate such patients with more advanced diabetes in order to be able to establish this point with confidence.

An advantage of our study is that we examined the effects of these preloads in patients with good overall glycemic control (HbA1c $\leq$ 7.9%), a group in which overall HbA1c is particularly dependent on managing postprandial glycemia [26,27]. There are, however, several limitations which should be appreciated. We did not evaluate the effects of varying the interval between preload administration and meal ingestion, and as discussed above, this may have differential effects depending on the nature of the preload. Guar, in particular, may have a greater effect to reduce postprandial glycemia the closer it is taken to the meal [23]. Furthermore, we did not compare different doses of whey or guar; varying the dose of each may have impacted on the glucose lowering effect. For example, 55 g whey preloads appear to be associated with greater glucose lowering than 25 g [12,28]. However, in this study we wished to focus on low-dose preloads in the interests of limiting both their energy burden and cost.

In summary, in relatively well-controlled type 2 patients, both low-dose whey and whey/guar preloads reduced the postprandial glycemic excursion in response to a high carbohydrate meal, associated with slowing of gastric emptying. The addition of guar to whey did not augment glucose-lowering compared to whey alone, but attenuated the secretion of GLP-1, insulin and glucagon. These observations indicate that further investigation on the efficacy of the whey/guar preload is warranted for postprandial glycaemic control in patients with more advanced type 2 diabetes or higher HbA1c.

Disclaimers

None.

Statement of authorship

L.E.W. conducted the study, including preparation of the protocol, subject recruitment, and data collection and analysis, and prepared the manuscript. L.K.P. supervised preparation of the protocol, and critically reviewed the manuscript. M.J.B., H.L.C., and J.G. assisted in subject recruitment and the performance of the study. T.W., K.L.J., and M.H. supervised preparation of the protocol, and critically reviewed the manuscript. C.K.R. conceived the study, supervised preparation of the protocol, and was responsible for final content of the manuscript. C.K.R. is the guarantor of this work and, as such, had full access to all data in the study and takes responsibility for the integrity of the data and accuracy of data analysis.

Sources of support

This study was funded by a grant awarded by the National Health and Medical Research Council of Australia (APP1066835). Omniblend Innovation (Victoria, Australia) supplied the whey and guar. L.E.W. was supported through a Dawes Scholarship, Royal Adelaide Hospital. T.W. and L.K.P. are supported by Royal Adelaide Hospital Research Committee Early Career Fellowships. K.L.J. is supported by a University of Adelaide Beacon Research Fellowship.

Conflicts of interest

Omniblend Innovation (Victoria, Australia) supplied the whey and guar preloads, but had no role in study design, analysis of data, or the decision to publish.

References

[1] FLAT-SUGAR Trial Investigators. Glucose variability in a 26-week randomized comparison of mealtime treatment with rapid-acting insulin versus GLP-1 agonist in participants with type 2 diabetes at high cardiovascular risk. Diabetes Care 2016;39:973–81.
[2] Monnier L. Is postprandial glucose a neglected cardiovascular risk factor in type 2 diabetes? Eur J Clin Invest 2000;30(Suppl 2):3–11.
[3] Standl E, Schnell O, Ceriello A. Postprandial hyperglycemia and glycemic variability: should we care? Diabetes Care 2011;34(Suppl 2):S120–7.
[4] Rayner CK, Samsom M, Jones KL, Horowitz M. Relationships of upper gastrointestinal motor and sensory function with glycemic control. Diabetes Care 2001;24:371–81.
[5] Chang J, Rayner CK, Jones KL, Horowitz M. Diabetic gastroparesis and its impact on glycemia. Endocrinol Metab Clin N Am 2010;39:745–62.
[6] Horowitz M, Edelbroek MA, Wishart JM, Straathof JW. Relationship between oral glucose tolerance and gastric emptying in normal healthy subjects. Diabetologia 1993;36:857–62.
[7] Gonlachanvit S, Hsu CW, Boden GH, Knight LC, Maurer AH, Fisher RS, et al. Effect of altering gastric emptying on postprandial plasma glucose concentrations following a physiologic meal in type-II diabetic patients. Dig Dis Sci 2003;48:488–97.
[8] Nauck MA, Heimesaat MM, Orskov C, Holst JJ, Ebert R, Creutzfeldt W. Preserved incretin activity of glucagon-like peptide 1 [7-36 amide] but not of synthetic human gastric inhibitory polypeptide in patients with type-2 diabetes mellitus. J Clin Invest 1993;91:301–7.
[9] Deane AM, Nguyen NQ, Stevens JE, Fraser RJ, Holloway RH, Besanko LK, et al. Endogenous glucagon-like peptide-1 slows gastric emptying in healthy subjects, attenuating postprandial glycemia. J Clin Endocrinol Metab 2010;95:215–21.
[10] Wu T, Rayner CK, Horowitz M. Incretins. Handb Exp Pharmacol 2016;233:137–71.
[11] Wu T, Zhao BR, Bound MJ, Checklin HL, Bellon M, Little TJ, et al. Effects of different sweet preloads on incretin hormone secretion, gastric emptying, and postprandial glycemia in healthy humans. Am J Clin Nutr 2012;95:78–83.
[12] Ma J, Stevens JE, Cukier K, Maddox AF, Wishart JM, Jones KL, et al. Effects of a protein preload on gastric emptying, glycemia, and gut hormones after a carbohydrate meal in diet-controlled type 2 diabetes. Diabetes Care 2009;32:1600–2.
[13] Fieseler P, Bridenbaugh S, Nustede R, Martell J, Orskov C, Holst JJ, et al. Physiological augmentation of amino acid-induced insulin secretion by GIP and GLP-I but not by CCK-8. Am J Physiol 1995;268:E949–55.
[14] Russo A, Stevens JE, Wilson T, Wells F, Tonkin A, Horowitz M, et al. Guar attenuates fall in postprandial blood pressure and slows gastric emptying of oral glucose in type 2 diabetes. Dig Dis Sci 2003;48:1221–9.
[15] Jenkins DJ, Goff DV, Leeds AR, Alberti KG, Wolever TM, Gassull MA, et al. Unabsorbable carbohydrates and diabetes: decreased post-prandial hyperglycaemia. Lancet 1976;2:172–4.
[16] O'Donovan D, Feinle-Bisset C, Chong C, Cameron A, Tonkin A, Wishart J, et al. Intraduodenal guar attenuates the fall in blood pressure induced by glucose in healthy older adults. J Gerontol A Biol Sci Med Sci 2005;60:940–6.
[17] Dall'Alba V, Silva FM, Antonio JP, Steemburgo T, Royer CP, Almeida JC, et al. Improvement of the metabolic syndrome profile by soluble fibre - guar gum - in patients with type 2 diabetes: a randomised clinical trial. Br J Nutr 2013;110:1601–10.
[18] Clifton PM, Galbraith C, Coles L. Effect of a low dose whey/guar preload on glycemic control in people with type 2 diabetes-a randomised controlled trial. Nutr J 2014;13:103.

[19] Ghoos YF, Maes BD, Geypens BJ, Mys G, Hiele MI, Rutgeerts PJ, et al. Measurement of gastric emptying rate of solids by means of a carbon-labeled octanoic acid breath test. Gastroenterology 1993;104:1640–7.
[20] Chew CG, Bartholomeusz FD, Bellon M, Chatterton BE. Simultaneous 13C/14C dual isotope breath test measurement of gastric emptying of solid and liquid in normal subjects and patients: comparison with scintigraphy. Nucl Med Rev Cent East Eur 2003;6:29–33.
[21] Wolever TM. Effect of blood sampling schedule and method of calculating the area under the curve on validity and precision of glycaemic index values. Br J Nutr 2004;91:295–301.
[22] Thazhath SS, Wu T, Bound MJ, Checklin HL, Jones KL, Willoughby S, et al. Changes in meal composition and duration affect postprandial endothelial function in healthy humans. Am J Physiol Gastrointest Liver Physiol 2014;307:G1191–7.
[23] Fuessl S, Adrian TE, Bacarese-Hamilton AJ, Bloom SR, Guar in NIDD. Effect of different modes of administration on plasma glucose and insulin responses to a starch meal. Pract Diab Int 1986;3:258–60.
[24] Holmer-Jensen J, Hartvigsen ML, Mortensen LS, Astrup A, de Vrese M, Holst JJ, et al. Acute differential effects of milk-derived dietary proteins on postprandial lipaemia in obese non-diabetic subjects. Eur J Clin Nutr 2012;66:32–8.
[25] Calbet JA, MacLean DA. Plasma glucagon and insulin responses depend on the rate of appearance of amino acids after ingestion of different protein solutions in humans. J Nutr 2002;132:2174–82.
[26] Riddle M, Umpierrez G, DiGenio A, Zhou R, Rosenstock J. Contributions of basal and postprandial hyperglycemia over a wide range of A1C levels before and after treatment intensification in type 2 diabetes. Diabetes Care 2011;34:2508–14.
[27] Monnier L, Lapinski H, Colette C. Contributions of fasting and postprandial plasma glucose increments to the overall diurnal hyperglycemia of type 2 diabetic patients: variations with increasing levels of HbA(1c). Diabetes Care 2003;26:881–5.
[28] Ma J, Jesudason DR, Stevens JE, Keogh JB, Jones KL, Clifton PM, et al. Sustained effects of a protein 'preload' on glycaemia and gastric emptying over 4 weeks in patients with type 2 diabetes: a randomized clinical trial. Diabetes Res Clin Pract 2015;108:e31–4.