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Sustained effects of a protein 'preload' on glycaemia and gastric emptying over 4 weeks in patients with type 2 diabetes: A randomized clinical trial

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ABSTRACT

We have shown that the capacity of 25 g whey preloads to slow gastric emptying and reduce postprandial glycaemia persists after 4 weeks regular exposure in patients with diet-controlled type 2 diabetes. This dietary strategy therefore appears feasible for larger clinical trials to evaluate beneficial effects on long-term glycaemic control.

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1. Introduction

Postprandial glycaemia is a key determinant of glycaemic control, particularly in patients with relatively modest elevation of HbA1c (less than ~7.5% (58 mmol/mol)) [1]. Both the rate of gastric emptying and the secretion of incretin hormones are important determinants of postprandial glycaemia [2].

We previously reported that a 55 g whey protein 'preload', given 30 min before a high carbohydrate meal, slowed gastric emptying, stimulated incretin and insulin secretion, and

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markedly attenuated postprandial blood glucose in patients with type 2 diabetes [3].

Adaptive changes might occur in gastric emptying with sustained protein intake, given that this has been reported for carbohydrate [4,5] and fat [6]. Therefore, we examined whether the effects of a whey preload are sustained with ongoing exposure.

2. Subjects and methods

Seven diet-controlled type 2 patients (3 male; age 60 ± 2 years; body mass index 31 ± 2 kg/m^2) were studied after giving written, informed consent, in a randomized, single-blind, and cross-over protocol, approved by the Royal Adelaide Hospital Human Research Ethics Committee.

Subjects consumed a chocolate-flavoured preload (100 ml water with either 25 g whey protein isolate (Murray Goulburn, Melbourne, Australia; 89 kcal) or 25 g chocolate-flavoured 'diet' sauce as a placebo (Cottee's, Southbank, Australia; 8 kcal), 30 min before each of the three main meals for 4 weeks, followed by a 2 week 'washout', and then the alternative preload for 4 weeks. Compliance was monitored by daily checklist and weekly telephone calls.

Participants were studied at ~0830 h after an overnight fast on four occasions, on the first and last day of each treatment period. Subjects consumed the preload ($t = -30$ min) followed by a mashed potato meal ($t = 0$ min) (65 g powdered potato (Deb, Epping, Australia) and 20 g glucose, reconstituted with 250 ml water (total carbohydrates 62 g; 314 kcal), labelled with 20 MBq ^{99m}Tc-sulphur colloid). Gastric emptying was assessed for 240 min using scintigraphy, and blood glucose concentrations measured by glucometer (Medisense, Abbott, Bedford, USA). Body weight, fructosamine (a measure of short-term glycaemic control [7]), and HbA1c were measured at each visit. Food consumption was recorded in a 3 day diet diary before each of the four study days [8] to evaluate energy intake.

Data (shown as mean ± standard error) were evaluated using repeated measures ANOVA and paired t tests; $P < 0.05$ was considered significant.

3. Results

Subjects consumed 98 ± 1% of scheduled preloads during both treatment periods.

Blood glucose at $t = -30$ and 0 min did not differ between the four study days. After the first preload dose, postprandial blood glucose was lower after whey than placebo (ANOVA treatment × time interaction, $P < 0.05$). Peak blood glucose was also reduced after whey (12.5 ± 0.8 mmol/L vs. 13.8 ± 0.5 mmol/L, $P = 0.005$). After 4 weeks exposure to each preload, blood glucose was again lower after whey than placebo (treatment × time interaction, $P < 0.05$), although peak blood glucose (12.7 ± 0.7 mmol/L vs. 13.3 ± 0.7 mmol/L, $P = 0.10$) was not significantly different. Blood glucose did not differ between the two whey days, or two placebo days.

After the first preload dose, gastric emptying was slower after whey than placebo (treatment × time interaction, $P < 0.0005$). This difference persisted after 4 weeks exposure (treatment × time interaction, $P < 0.0005$). Gastric emptying did not differ between the two whey days, or two placebo days.

At the beginning of each treatment period, fructosamine did not differ between whey and placebo (259.3 ± 16.4 vs. 257.3 ± 11.2 μmol/L). After 4 weeks, fructosamine tended to be lower after whey than placebo (252.9 ± 15.2 vs. 279.4 ± 9.6 μmol/L, $P = 0.06$), without differing significantly before and after either whey or placebo interventions. HbA1c did not differ between whey and placebo at baseline (6.0 ± 0.3 vs. 6.0 ± 0.2%) (42 ± 3 vs. 42 ± 2 mmol/mol), or after 4 weeks treatment (5.9 ± 0.2 vs. 6.0 ± 0.2%) (41 ± 3 vs. 42 ± 2 mmol/mol).

Energy intake (daily mean over 3 days, excluding the preload drinks) did not differ significantly between whey and placebo treatments, either before the intervention (1942 ± 131 vs. 2038 ± 146 kcal), or during the 4th week (1867 ± 85 vs. 1895 ± 161 kJ); nor was there any difference in body weight between whey and placebo preloads at baseline (89.7 ± 6.8 vs. 89.4 ± 6.8 kg), or after 4 weeks (88.8 ± 7.1 vs. 89.3 ± 7.0 kg). Fig. 1

4. Discussion

This study has established that the effect of a whey preload to reduce glycaemia after a subsequent meal is sustained after four weeks exposure in type 2 diabetes, i.e. there were substantial differences in postprandial blood glucose concentrations from placebo, but no difference between the first and last doses of whey. Moreover, we observed that excellent compliance is achievable.

The dose of whey was lower than in our previous acute study [3], in order to minimize additional energy intake; this likely explains the lesser reduction in peak blood glucose (~1 mmol/L vs. 2 mmol/L). Although the peak glucose (~13 mmol/L) appears relatively high for well controlled type 2 patients, it is consistent with our previous study [3], and explained by the high carbohydrate content of the meal. Neither fructosamine nor HbA1c were significantly lowered after 4 weeks of whey, when compared to placebo, possibly due to the small number of patients, low HbA1c at baseline, and relatively brief intervention. It would also be important to determine in an adequately powered trial whether subjects compensated for the additional energy intake of the whey preload.

Unlike carbohydrate [5] or fat [6], we did not observe any adaptation of the slowing of gastric emptying in response to protein; this might relate to the relatively low protein content of the test meal, as adaptation appears to be macronutrient specific [4]. It should be noted, however, that slowing of emptying is probably not the only mechanism by which glycaemia was lowered; we previously showed that whey preloads also stimulate insulin secretion acutely [3], although we did not measure insulin in the current study.

Our observations support the concept of whey preloads as a long-term management strategy, which should be explored with larger clinical trials in patients with type 2 diabetes.