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OMNIBLEND (A PRE-MEAL DRINK) AND IMPROVED GLYCAEMIC CONTROL IN TYPE 2 DIABETES

– THE CHRONIC STUDY

Introduction:

Large preloads of protein and fat have been shown to lower glucose after a carbohydrate-rich meal in people with type 2 diabetes but add a considerable energy burden. Low calorie preloads [<5% of daily energy intake] were tested in people with prediabetes and with type 2 diabetes.

We previously performed an unblinded randomised crossover study with two placebo days and two active treatment days. Glucose was measured for 3 hours with fingerprick samples as well as continuous glucose monitoring [CGMS]. Twenty-four subjects with pre-diabetes or moderately controlled type 2 diabetes [fasting glucose < 10 and HbA1c < 8.5%] were recruited. The preload (80kcal) contained 17 g whey protein plus 3 g lactose and 5 g guar, and 1 g flavour material [including sucralose] dissolved in 150 ml cold water or 150 ml cold water with no additives. The breakfast test meal consisted of 2 slices of bread, margarine and jam [3 slices for men] with the test drink 15 minutes beforehand.

Peak fingerprick glucose was reduced by 2.1 mmol/L at 45 min [$p < 0.0001$]. Average fingerprick glucose over 3 hours was reduced by 0.8 mmol/L [$p = 0.0003$]. There was no difference between those with diabetes or prediabetes or those on medication or not on medication (Clifton et al 2014)

This study was designed to see if post meal glucose lowering would translate into a lowering of HbA1c over 3 months in a randomised, unblinded controlled trial

Methods:

141 people with pre-diabetes or type 2 diabetes for whom the drink limits the rise in blood glucose following a meal (meal test) were asked to take at least one protein/fibre drink per day for 3 months, and for comparative purposes, be monitored for a further 3 months when not consuming the protein/fibre drink i.e. the study will last for a total of 6 months. The order of drinks or no drinks was randomised.
Prior to beginning the chronic study a 1½ hour meal test was performed with 2 slices of bread with jam to ensure the protein/fibre drink limits the rise in blood glucose levels after a meal to a maximum increase of 3mmol/L. If it did not, then the volunteer did not enter the chronic study.
At the same time as blood was collected for the HbA1c blood test, blood was collected for a liver function test and full blood count, but only during the 3 and 6 month blood tests and not the baseline tests.

Other data that was collected included body weight, blood pressure, compliance using a sachet count and palatability of the supplement. We aimed to have 120 people finish the

study. This would have enabled us to detect a change in HbA1c of 0.25% ($p<0.05$, 80% probability)

If the protein/fibre mix causes abdominal disturbances a drink with a lower amount of fibre or no fibre at all was substituted.

Volunteers had the **option** of wearing the continuous glucose monitor for 7 days when starting drinking the drink, and again for 7 days when finishing drinking the drink (i.e. two 7 day periods in total). Volunteers were required to measure and record fingerprick glucose levels 4 times a day, as well as recording food and drink whilst wearing the glucose monitor.

Results:

HbA1c

127 volunteers had a baseline HbA1c but 21 dropped out after the baseline test-either for reactions to the drink or for commencing excluded medication or lack of time/interest.

Medication

61 volunteers had prediabetes (based on HbA1c<6.5% and no diabetes medication) and 66 had type 2 diabetes. 5 volunteers said they had type 2 diabetes but their HbA1c was<6 in all cases. 45 volunteers were taking metformin, and 12 were taking a sulphonylurea (7 with metformin), 3 were taking gliptins (2 with metformin), 1 PPARG activators (with metformin) and 1 was taking glucobay (with metformin) and 16 were diet controlled

64 volunteers were randomised to take the drinks in the first 3 months and have no treatment in the second 3 months. 44 completed baseline , 3 and 6 months while 10 dropped out between 3 and 6 months. 10 dropped out after the baseline measure. The change between baseline and 3 months was a rise in HbA1c of 0.05%. The change between 3 months and 6 months was a fall of 0.07%. Between baseline and 3 months 20 people had an HbA1c fall and 34 an HbA1c rise. Between 3 and 6 months 26 people had an HbA1c rise and 18 an HbA1c fall.

63 volunteers were randomised to take the drinks in the second 3 months. 5 dropped out after 3 months while 11 dropped out after baseline. 47 completed all 3 phases. HbA1c rose by 0.02% in the first 3 months and rose by 0.06% in the second 3 months. In the second 3 months 17 people had a fall and 32 people a rise in Hba1c

Thus overall there was no change at all in HbA1c and statistical no difference between the number of responders and non responders.

Examining predictors of response ***having early type 2 diabetes on no medication predicted a greater number of responders (HbA1c fall) 11/16 during the drink phase versus 6/16 during the control phase (Chi squared p=0.07)***. Average consumption of sachets 85 over 3 months out of a maximum of 93 (ie>90%) in this more responsive group was no different from the whole group-average 87.

All volunteers in the chronic study either had 2-3 days of comparison of a preload with a water meal test as part of the acute study (n=20) or had a 60 minute single premeal test (n=108) with no control phase. There was no correlation between 60 minute glucose in any test and change in HbA1c in the chronic study. Similarly those who had a positive result in

the acute study (compared with water) did not necessarily have a positive change in the chronic study. In the sensitive group (HbA1c>6.5% and no medication=17) there was no correlation between 60 min glucose level and change in HbA1c. Within this group only 3 acute participants were included. The one with a negative response in the acute test had a rise in HbA1c while the other 2 had a fall in HbA1c

Liver function tests.
11 volunteers had either an elevated GGT or ALT or both. There was no effect of the drink on these variables which did not change significantly between the two time points (3 and 6 months).

Weight.
Weight went down during both phases by 1.4kg in the shake phase and by 0.8kg in the control phase (NS).

Discussion.

One premeal protein/fibre drink has the ability to lower two hour area under the glucose curve by about 35-37% with a peak reduction of 1.5 mmol/L. Over 4 hours the reduction is less at 21%. To predict the effect on HbA1c it is total glycemic exposure that is important so over 2 hours this is a reduction of 11.5% and over 4 hours 4.6%. Thus if a high carbohydrate meal was preceded by a protein/fibre drink then over the 12 hours of 3 meals/day total glucose exposure would be reduced by 4.6% . During the other 12 hours one would expect no change in average glucose levels. Thus the maximum change in HbA1c would be <5%. For individuals in the optimum group with an HbA1c of 6.5-7.5% on no medication then the expected change in HbA1c would be about 0.3-0.4 % which we were powered to see with 120 completers but only 106 completed the study.

If we examined studies that have reduced the amount of carbohydrate in the diet and substituted it with protein or fat one meta analysis (Kodama 2009) showed reduced 2hr glucose and insulin and lower day-long glucose but no significant change in HbA1c but the longest study was 6 weeks long. A second meta analysis (Kirk 2008) which only examined North American studies showed a significant reduction in HbA1c with a reduced carbohydrate diet (p=.013) with a regression equation of % (change in HbA1c =-23.6 +44 (% carbohydrate calories). Thus changing from 60% carbohydrate to 50% carbohydrate would be predicted to reduce HbA1c by about 2% (ie an absolute change in HbA1c of about 0.13-0.14%) .This value is in line with another meta analysis from Ajala et al 2013 who found an overall effect of low carbohydrate diets on HbA1c with a reduction of 0.12%. The effect of diet on HbA1c when no weight loss has occurred is heavily dependent on the degree of glycemic control and in those with a well controlled HbA1c of <7%, postprandial (and thus diet composition amenable) glucose levels contributes a much higher proportion to the HbA1c (60-80%) compared with those with poorly controlled HbA1c and fasting sugar levels of 10-11mmol/L (Woerle 2007, Riddle 2011, Fysekidis 2014).

Even if HbA1c is unchanged in an individual a peak postprandial reduction of 1.5 mmol/L may lead to reduced atherosclerosis (Su 2011) and reduced primary CVD events (Bonora 2002, Meigs 2002, Ceriello 2006, Leiter 2007) although this may not apply in secondary prevention (Raz 2009, Siegelar 2011). In this study, the Heart 2D study, patients with type 2 diabetes and a recent myocardial infarction were randomised to basal insulin or insulin targeted on postprandial glucose. The basal group had a lower fasting glucose (1.1 mmol/L difference) and higher postprandial glucose (0.8 mmol/L different) and overall control , as reflected in HbA1c was the same. CVD events were the same, suggesting if postprandial glucose is important it may needed to be addressed well before atherosclerotic events have occurred.

Acarbose which reduces postprandial glucose reduced the relative risk of CV events by 49% over 3.3 years versus placebo in patients with impaired glucose tolerance (2.2% vs 4.7%; P = 0.03) and by 35% over > or =1 year in patients with type 2 diabetes (9.4% vs 6.1%; P = 0.006) (Chiasson 2003)

Acarbose 100mg lowers the average post meal glucose over 4 hours by about 50% compare with placebo (Rosak 2002). Weighed mean change in 1 hour glucose varied from 1 to 4.5 mmol/L depending on dose (http://www.drugs.com/pro/acarbose.html) so the protein/fibre drink is equivalent to 25mg of acarbose.

Regardless of the effect on HbA1c the drink contains fibre and protein so may have advantages in weight control in long term use because of its potential satiating effect. There is no weight gain in volunteers over 3 months with the drink but also no clear weight loss.

Conclusion. One drink/day has no effect overall on HbA1c but responders to the drink were over represented in the no medication early type 2 DM group. Further studies need to be done consuming the drink 2-3 times/day in this particular group.

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