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Alginate reduces uptake of cholesterol and glucose in overweight human subjects: a pilot study.

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Abbreviations

BMI – Body Mass Index
TAG - Triacylglyceride
AUC – Area under curve

ABSTRACT

Dietary fibres are of particular interest in the prevention and management of obesity and consequent pathologies. Amongst the proposed mechanisms of action of fibre are the modulation of nutrient uptake from the small intestine. We have used a cross-over study design in human subjects to monitor the uptake of glucose, cholesterol and triacylglycerides (TAG) in human subjects with normal and high body mass index (BMI). Our pilot data demonstrate that uptakes of glucose, TAG and cholesterol are all increased with increasing percentage body fat, and that a 1.5g dose of a strong-gelling alginate may restore uptake of cholesterol and glucose to normal levels.

Keywords:

Alginate, uptake, glucose, cholesterol, BMI, human

| 1. INTRODUCTION

Diets rich in fibre are thought to be preventative in the pathogenesis of obesity [1,2]. This has variously been attributed to the low energy density of high fibre diets, a reduced rate of gastric emptying and/or potential for enhanced gastric stretch following fibre ingestion. However, the role that dietary fibre plays in the prevention of weight gain might be due in part to the association it has with improvements in the lipid profile and glucose handling. Populations with high fibre intakes have lower serum cholesterol. The reduced uptake of cholesterol [3] increased excretion of lipids as faecal bile acid [4,5], coupled with reduced absorption of glucose - leading to altered insulin secretion and therefore lowered cholesterol synthesis - have all been presented as potential candidates for the mechanism of action of fibre in relation to cholesterol lowering.

Wu & Peng [4] investigated various dietary fibres (konjac, pectin, algin and agar) in rats on lipid-rich diets. All the fibres similarly prevented a rise in serum cholesterol (with no change in triglyceride). In addition, the daily output of faecal bile was increased for all four fibres when compared to the normal group and control group. Rats fed on guar gum-rich diets for sixty days showed significantly reduced levels of blood serum cholesterol and triglyceride compared to control rats. These findings were coupled with reduced blood serum glucose for the first month of the experiment. Studies in humans involving dietary supplementation with soluble fibre have demonstrated cholesterol-lowering effects [7,8,9]. These effects seem to be specific to fibre preparations and not universal [10].

Some fibres are additionally thought to modulate glycaemia. The glycaemic response to a carbohydrate load was significantly reduced in healthy female volunteers following addition of Nori seaweed [11]. Likewise Lavin and Read [12] demonstrated significantly reduced peak glucose and 2-hour area under the curve plasma glucose in healthy male volunteers following a 30% glucose drink with 2% guar gum compared to control. In a study of free-living, healthy adults, fasting glucose and total cholesterol levels were significantly reduced following a 3 month prescribed high fibre diet, however, fasting triglyceride levels remained unaltered during this time [13]. In general, soluble fibre does not seem to have potential triglyceride lowering properties [10 13]. However, some animal studies [6] and human studies [15] suggest otherwise. Jenkins et al. [15] conducted a randomised, controlled two-way crossover study to investigate the effect of a high fibre diet on the lipid profile of hyperlipidaemic subjects, demonstrating a significant total cholesterol and triglyceride-lowering effect of the high-fibre diet compared to the control diet.

The polyuronic saccharide sodium alginate is a fibre isolated from the cell walls of brown algae and some bacteria [16]. Alginates have wide ranging applications in the food and pharmaceutical sectors [17]. The modifiable primary structure of alginates determines their physical and chemical properties [17] and therefore their usefulness in various settings. Alginate is capable of forming a cross-linked gel network in the presence of divalent cations such as calcium.

To date there are few studies on the effect of sodium alginate on lipaemia and glycaemia. There is an inverse linear relationship between supplementary

dietary fibre intake and plasma cholesterol for alginate and an associated increase in total faecal bile levels [5]. Kimura et al. [18] examined a range of alginate formulations in rats, showing increased cholesterol excretion and improved glucose tolerance. Parallel findings with studies of ileostomy patients support an increase in fatty acid excretion occurring in sodium alginate supplementation on a low-fibre diet [19]. Wolf *et al* [20] demonstrated a fall in peak glycaemia following ingestion of a viscous alginate drink. Williams *et al* [21] showed that incremental peak glucose was significantly lower ($p < 0.001$) and positive incremental area under the curve (AUC) (T+180mins) was significantly reduced ($p < 0.01$) after consumption of an alginate-containing bar. Torsdottir et al. [22] showed similar results in type-2 diabetic males.

The literature suggests that sodium alginate may have particular value in management of obesity through alterations in nutrient uptake. This pilot study set out to use a cross-over design to address whether a sodium alginate beverage, specifically formulated to gel within the gastrointestinal tract, could modulate normal physiological lipaemic, glycaemic and cholesterolaemic responses in subjects across a range of body compositions. The data indicate that uptake of all three nutrients is perturbed in overweight subjects relative to their normal counterparts and that the increased uptake of cholesterol and glucose can be reduced to normal levels by alginate. This offers scope for the use of alginate in the management of obesity and related comorbidities including diabetes.

M2. METHODS

2.1 Subjects

The study was approved by Sheffield Hallam University Ethics Committee (reference: OMREC/FIRC/2006/01). Fourteen healthy male subjects were recruited via e-mail circulation lists and electronic message boards in accordance with previously used criteria [23]. Subjects gave informed consent to take part in the study. The subject profile is shown Table 1.

2.2 Design

The study was conducted as a randomised, single-blinded, controlled, two-way crossover trial. On the intervention arm of the trial, subjects ingested a 100ml, strong-gelling sodium alginate-based drink. This formulation included 1.5g of sodium alginate in the presence of calcium carbonate [23]. A comparably viscous 100ml drink containing 0.25g of hydroxypropyl methylcellulose was used as a control. Both drinks were vanilla flavoured. A washout period of a minimum of 7 days was set in order to ensure there was no carryover effect from treatment to control or vice-versa. Subjects were given a standard frozen, microwavable meal, consisting of vegetable lasagne, steamed mixed vegetables and syrup sponge-pudding with custard, to consume on the evening prior to the study. Subjects were asked to consume the entire meal and nothing else between 6pm and 10pm on the evening prior to the study. From 10pm, subjects undertook a 10-hour fast before travelling to the study to begin the acute phase of the experiment. Subjects were asked

to minimise energy expenditure throughout this period. These conditions were upheld for each arm of the study

Anthropometric measures were made on both experimental mornings of the study prior to breakfast; height was measured using a free-standing portable stadiometer and body fat percentage and weight were determined using Tanita BF-626W scales.

At 9am on study days a controlled breakfast (similar to that described by other workers [24, 25]) of 60g of Kellogg's Crunchy Nut CornFlakes, 125g semi-skimmed milk and 200g UHT orange juice was consumed by each subject. Subjects were thereon limited to consumption of water (maximum one litre) and sedentary activity until administration of 100ml of the preload drink (either the alginate formulation or control) at noon.

In order to allow measurement of lipaemic and glycaemic response, the test-lunch contained sufficient fat and carbohydrate to illicit a response and, to ensure constancy of intake for subsequent uptake measurements, all subjects were provided with the same portion size. The test lunch was a meal of 100g Sacla™ Italia Vine-ripened Tomato & Mascarpone Stir Through sauce: 300g cooked penne pasta. The meal provided 57%, 13% and 30% of total energy from carbohydrate, protein and fat respectively as analysed by NetWISP (version 3.0 for Windows, Tinuviel Software, Anglesey, UK).

2.3 Blood collection and analysis

Capillary blood samples were taken from the finger at 0 minutes (15 minutes prior to preload) and at the following intervals (mins): 30 (pre-prandial), 105, 120, 135, 150, 165, 180, 195, 225. Samples were taken using an Accu-check® Softclix® Pro lancing device. Two 30µl samples were collected in uncoated capillary pipettes and applied immediately to Reflotron® reagent strips for cholesterol and for triacylglycerides (TAG). The Reflotron® Plus (Bio-Stat Diagnostic Systems, Cheshire, UK), a reflectance photometer, was then used to analyse each sample. A final droplet sample was collected using OneTouch® Ultra® Test Strips with FastDraw™ design. This was analysed using the OneTouch® Ultra® Blood Glucose Monitoring System (Lifescan Inc., Bucks, UK).

2.4 Statistical analysis

Measurements made of blood parameters (e.g. glucose) across time allowed the generation of a curve from which area-under-the-curve (AUC) data (REF) could be obtained. All blood measures were converted to change from baseline area under the curve (AUC).—AUC data were generated in accordance with the trapezoidal rule (with subtraction of the basal values) as previously described by Porcellati et al. [26] using NCSS (Hintze, 2004, NCSS and PASS Number Cruncher Statistical Systems, Kaysville, Utah.). Initial analyses used a Paired samples t-tests were used to compare findings—AUC values between the intervention and control arms of the trial (SPSS, version 13.0 for Windows, SPSS Inc., Chicago, IL, USA). In order to evaluate the effect across differing bodyfat measures, Pearson Product Moment Correlations (REF [27] we) were

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performed to demonstrate the relationship between body fat percentage and nutrient uptake (SPSS, version 13.0 for Windows, SPSS Inc., Chicago, IL, USA). All graphical presentations were produced using SPSS (version 13.0 for Windows, SPSS Inc., Chicago, IL, USA). [Data with a probability of <0.05 were considered significant.](#)

R3. RESULTS

3.1 Initial analyses

Measures were made of circulating nutrients following a balanced meal in all subjects after either the alginate or control preload. Data were analysed by subject as the change from baseline AUC (for each whole blood measure following the meal).

Initial analyses explored differences in AUC and peak levels between the alginate and control groups. We observed no significant differences in AUC cholesterolaemia, triglyceridaemia or glycaemia (over 225 minutes) following an alginate preload compared to the control (paired-samples *t*-test: $p=.764$, $p=.874$ and $p=.874$ respectively, data not shown). Additionally, there were no significant differences following alginate compared to the control for peak blood cholesterol, triglycerides or glucose (paired-samples *t*-test: $p=.075$, $p=.895$ and $p=.687$, data not shown). These preliminary analyses predicated on the assumption that uptake would be unaffected by body composition. However, when this factor was taken into account with the analysis, significant differences in response to alginate versus control were observed.

3.2 Alginate modulates uptake of cholesterol and glucose uptake, but not TAG uptake in a body-composition-dependent manner

We observed a significant positive correlation between AUC cholesterolaemia and body fat percentage ($r= 0.59$, $P=0.026$; Fig 1A and D) following preloading with the hypromellose control, indicating that with increasing body fat subjects had greater uptake of cholesterol from a meal of fixed nutritional content. Following alginate ingestion, the positive significant correlation

between AUC cholesterolaemia and body fat percentage was weakened and reduced to a non-significant level ($r=0.14$, Fig 1A and D).

When subjects were grouped by BMI, significant attenuation of mean peak blood cholesterol was seen following alginate ingestion in subjects with an overweight/obese BMI ($n = 5$) compared to the control (paired-samples t -test, $p=.039$). No such significant finding was demonstrated for subjects with healthy BMIs ($n = 9$).

Figure 1B shows correlation between AUC glucose and body fat percentage. In this analysis the control group showed a strong positive correlation between total glucose uptake and body fat ($r=0.32$) after preload with the hypromellose. When alginate was used as the preload, the strength of the correlation was reduced ($r= 0.15$), demonstrating the potential to repair the altered glycaemic response of the overweight/obese subjects to the levels seen in normal subjects. Analyses of the data for triacylglyceride showed no change to the correlation observed in the control condition compared to with alginate (Fig 2C and D).

D4. DISCUSSION

The early onset of metabolic syndrome is marked by increasing insulin resistance and it is recognised that this will result in altered uptake kinetics for glucose with consequences for impaired maintenance of blood glucose and appetite. Our findings support this literature and suggest that our study cohort showed altered glucose uptake in the high body-fat group by comparison with the normal body fat group. Three cross-sectional studies have reported that subjects with high BMI have elevated levels of blood cholesterol [268, 279, 2830]. We report herein and for the first time that cholesterol uptake is altered in subjects with elevated BMI or body fat. This novel observation suggests a contributory mechanism to the incidence of elevated blood cholesterol and thereby many of the co-morbidities of metabolic syndrome, including coronary heart disease and other vascular diseases. We also noted that there was altered uptake kinetics of triacylglycerol with increasing body fat. Taken together these data may imply a common underlying cause for altered uptake in subjects with high body fat.

Having identified the link between altered body fat and nutrient uptake, we have addressed the potential of alginate to modulate this effect. Using a meal of fixed nutritional content in order to control intake level, and a randomised, blinded, cross-over trial structure, we have shown that the strong correlations between uptake and body fat are reduced in strength by preloading with this alginate formulation. The fact that the intervention removes the correlation observed in the absence of the preload suggests alginate is acting to restore

rates of uptake in subjects with elevated body fat to the levels of uptake in normal subjects for both cholesterol and glucose.

It is unlikely that this will be attributable to altered rate of gastric emptying as we saw no alteration in time to peak uptake with either nutrient, as the timing and size of the TAG uptake peak was the same with and without alginate, and the observations held for AUC (an indicator of total uptake over time). Alginate is therefore likely acting at the level of small intestinal uptake by altering the availability of nutrients to active uptake mechanisms.

We have therefore demonstrated the potential of alginate to offset pre-clinical metabolic syndrome symptoms including insulin-resistance; to treat type II diabetes mellitus; treat hypercholesterolaemia and consequently reduce risk of development of cardiovascular disease. Following studies showing the efficacy of this alginate preparation in modulating calorie intake [23], this study suggests that alginate may modulate appetite through reduction in post-prandial glucose spiking and be highly effective in overweight and obese subjects.

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Figure legends

Figure 1. Relationships between nutrient uptake and body composition.

14 subjects were fed a meal of fixed nutritional value after a preload of either alginate or control. Uptakes of glucose, cholesterol and TAG were measured at intervals for 195 minutes postprandially. Uptake was calculated as total AUC for each curve. Panel A shows correlations between total AUC for cholesterol and % body fat for subjects consuming the control preload (open circles) and alginate (filled circles). Correlation curve for control is shown as a dotted line and for alginate as a solid line. Panel B shows the same analysis for glucose. Panel C shows the same analysis for TAG. Panel D summarises the [Pearson's Correlation coefficients for](#) curves in Panels A-C.

Table 1. Study group characteristics

[Table 2. Pearson's Correlation coefficients for Total AUC versus Bodyfat.](#)

[Correlation coefficients \(r values\) are shown for the correlations shown in figures 1a-1c.](#)

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