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Inulin and oligofructose: effects on lipid metabolism from human studies

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Although convincing lipid-lowering effects of the fructo-oligosaccharide, inulin, have been demonstrated in animals, attempts to reproduce similar effects in man have produced conflicting findings. This may be because of the much lower doses which can be used due to the adverse gastrointestinal symptoms exhibited by most subjects consuming in excess of 15 g/d. There are nine studies reported in the literature which have investigated the response of blood lipids (usually total and LDL-cholesterol and triacylglycerol) to inulin or oligofructose supplementation in human volunteers. Three have observed no effects of inulin or oligofructose on blood levels of cholesterol or triacylglycerol, three have shown significant reductions in triacylglycerol, whilst four have shown modest reductions in total and LDL-cholesterol. Studies have been conducted in both normo- and moderately hyperlipidaemic subjects. Differences in study outcomes do not appear to be due to differences in the type or dose of oligosaccharides used nor the duration of the studies. Because animal studies have identified inhibition of hepatic fatty acid synthesis as the major site of action for the triacylglycerol lowering effects of inulin and oligofructose, and because this pathway is relatively inactive in man unless a high carbohydrate diet is fed, variability in response may be a reflection of differences in background diet or the experimental foods used.

Triglyceridemia: Inulinemia: Inulin: Oligofructose

Introduction

Recent evidence has highlighted not only total cholesterol (TC) but also triacylglycerol (TAG) as a lipid risk factor for coronary heart disease. Although cholesterol is undoubtedly the major lipid component of foam cells and of the mature atherosclerotic plaque, there is now much evidence to support the proposition that elevated blood triacylglycerol levels lead to the generation of a blood lipid profile that is strongly linked with increased risk of cardiovascular disease (Williams, 1997). The key features of the lipid profile are moderately raised TAG, low HDL-cholesterol and raised small, dense LDL-cholesterol. Concentrations of TAG-rich remnant particles (chylomicron or VLDL remnants) are also usually elevated. Individuals with this collection of lipid abnormalities, which has been termed the atherogenic lipoprotein phenotype (ALP), have a 3–6-fold greater risk of CVD (Griffin *et al.* 1994). Furthermore an estimated 15–25 % of the middle aged male population of developed countries may be affected by this disorder, the aetiology of which has been linked with a more sedentary life style and high fat diets.

There is much evidence to support the view that insulin resistance is the primary metabolic component which leads to excessive synthesis and secretion of VLDL and impaired removal of both chylomicron and VLDL particles and elevated blood triacylglycerol levels. Evidence that impaired TAG tolerance and elevated TAG levels are the key lipid abnormality of a dyslipidaemia linked with a markedly higher risk of CVD, has generated a great deal of interest in possible dietary strategies that can reduce circulating TAG levels and which might also have beneficial effects in terms of insulin resistance. Indications that dietary inulin and oligofructose may offer such a possibility were raised by studies in rats that showed markedly reduced fasting TAG concentrations when fed diets containing significant amounts (50–200 g/kg of rat chow) of oligofructose (Roberfroid, 1993). Dramatic reductions in serum triacylglycerol levels have been reported in rats consuming relatively high doses of oligofructose, although reductions in cholesterol have only been seen with long-term feeding (Delzenne *et al.* 1993; Fiordaliso *et al.* 1995). Recent studies have shown the effects on serum triacylglycerol to be due to reduced secretion of VLDL particles from the liver and to be associated with reduced

Abbreviations: CVD, cardiovascular disease; NIDDM, non-insulin dependent diabetic; TAG, triacylglycerol; TC, total cholesterol.

Note: For the definition of the terms inulin and oligofructose please refer to the introductory paper (p. S139) and its footnote.

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Table 1. Studies of effects of inulin or oligofructose on blood lipids in humans — outcomes from studies showing no effect of treatment

Author	Subjects	Fructan	Dose (g/d)	Study design	Duration (weeks)	Vehicle	Changes observed in: Blood lipids	Glucose
Luo *et al.* 1996	12 M normo-lipidaemic	Oligofructose	20	DB crossover	4	100 g biscuits	NS	NS
Pedersen *et al.* 1997	66 F normo-lipidaemic	Inulin	14	DB crossover	4	40 g margarine	NS	N/A
Alles *et al.* 1999	20 M and F NIDDM	Oligofructose	15	DB crossover	3	Powder with yoghurt	NS	NS
Mean			16		3·7			

M=male, F=female, NIDDM=non-insulin dependent diabetes, DB=double blind, NS=non-significant, N/A=not assessed.

Table 2. Studies of effects of inulin or oligofructose on blood lipids in human volunteers — outcomes from studies showing a positive effect on blood lipids

Author	Subject	Fructan	Dose (g/d)	Design	Duration (weeks)	Vehicle	Changes in: Blood lipids	Blood glucose
Yashashati *et al.* 1984	8 M and 10F NIDDM	Oligofructose (from sucrose)	8	DB, Parallel	2	coffee drink canned coffee jelly	↓ TC ↓ LDLC	↓ glucose
Hidaka *et al.* 1991	37 (M & F) hyper-LP	Oligofructose (from sucrose)	8	DB, Parallel	5	Confectionary	↓ T-C	
Davidson *et al.* 1998	21 M and F hyper -LP	Inulin	18	DB crossover	6	Chocolate bar/paste or coffee sweetner	↓ LDLC ↓ T-C	
Jackson *et al.* 1999	54 M and F moderately raised cholesterol	Inulin	10	DB Parallel	8	Powder added to drinks, food	↓ TAG	↓ insulin
Brighenti *et al.* 1999	12 M normo-LP	Inulin	9	Sequential	4	Breakfast cereal	↓ LDL-C ↓ TAG	NS
Causey *et al.* 2000	Hyper -LP	Inulin	18	DB crossover	3	Ice cream	↓ TAG	NS
Mean			12·2		4·6			

Hyper -LP=hyperlipidaemic, normo-LP=normo lipidaemic, ↓=reduced significantly. Other abbreviations as in Table 1.

activity and gene expression of the key regulatory enzyme, fatty acid synthetase (Kok *et al.* 1996*a*,*b*). Some of the studies have also shown lower fasting and postprandial insulin concentrations in animals fed levels of fructo-oligosaccharide (FOS) that are effective in reducing circulating TAG levels.

Lipid responses to inulin and oligofructose in human volunteers

Although the data obtained from animal studies suggest convincing lipid lowering properties of oligofructose, much less information is available from human studies, where the doses which can be applied are much lower than those which have been used to elicit effects in animals. To date, a total of nine studies that have investigated effects of inulin or oligofructose on blood lipids in humans have been reported in the peer reviewed literature (Tables 1 and 2). Although some of the earlier studies used relatively small numbers of subjects, more recent trials have been conducted on larger numbers of subjects, using studies of robust design and levels of inulin or oligofructose close to the upper limits of gastrointestinal tolerance for most individuals. Tables 1 and 2 show the key features of studies that have shown negative and positive outcomes, respectively, for the effect of inulin or oligofructose on blood lipids.

Luo and co-workers (1996), investigated effects of oligofructose (20 g/d) fed as 100 g cookies a day in a randomised cross-over design with treatment periods of 4 weeks (Table 1). Sucrose was used as placebo. No changes in serum triacylglycerol, cholesterol or apolipoproteins were observed in either the treatment or placebo periods, although there was a strong trend for free fatty acid (FFA) concentrations to be reduced on oligofructose. Pedersen *et al.* (1997) reported no effect on blood lipids of a daily intake of 14 g inulin added to a low fat spread for a period of 4 weeks (Table 1). The study was a double-blind randomised cross-over design in sixty-six young healthy women. Although HDL cholesterol and the LDL:HDL cholesterol ratio were lower at the end of both the control and test (inulin) periods, there were no significant differences in blood lipids between placebo and inulin. Although this was a rigorously designed study with adequate statistical power, the fact that subjects were required to consume 40 g of spread per day (30 g/d fat), (approximately twice the normal level of spread intake and 50 % of total fat intake for young women), may have contributed to the negative findings observed in this group. More recently Alles *et al.* (1999) conducted a study using 15 g/d oligofructose (fed as powder in a low fat yogurt), in twenty male and female non-insulin dependent diabetic (NIDDM) subjects (Table 1). No effects on blood lipids or glucose were observed over a 3-week treatment period.

Subjects with NIDDM who were administered oligofructose (from sucrose) in a packed coffee drink or coffee jelly for 14 days (Table 2) showed reductions in total, (8 %) and LDL cholesterol (10 %), compared with a control group given sucrose in the same food vehicles (Yamashita *et al.* 1984). No effects on other serum lipids or on blood glucose concentrations were observed. Similar reductions in blood cholesterol were reported to have been observed in a group of Japanese subjects with hyperlipidemia (Hidaka *et al.* 1991). More recently Davidson *et al.* (1998) in a randomised cross-over trial in subjects with modest hyperlipidemia, showed significantly lower total and LDL concentrations during inulin compared with placebo phases, but the authors reported no effects on HDL cholesterol or serum triacylglycerol concentrations. In a study conducted on fifty-eight middle aged subjects with moderately raised blood lipid concentrations, subjects consumed 10 g/d of inulin or placebo in a powdered form which could be added to beverages, soups, cereals, etc. (Jackson *et al.* 1999). There were no significant changes in total, LDL or HDL cholesterol or apolipoproteins B and A, in either of the groups over the 8-week intervention. However, serum triacylglycerol levels were 19 % lower after intervention in the inulin treated group and values were significantly lower than in the control group. Subjects were chosen for their modestly raised triacylglycerol values at baseline and the study was conducted over a longer period than any of the previous human studies. Brighenti *et al.* (1999), also observed significantly lower triacylglycerol and cholesterol concentrations in young male volunteers who consumed 9 g inulin added to a rice breakfast cereal for a period of 4 weeks and levels remained significantly lower 4 weeks after the end of the inulin phase. Total cholesterol and LDL cholesterol levels were reduced by 5 % and 7 % respectively with inulin compared with placebo. In the group as a whole, strong and statistically significant associations were observed between faecal secondary bile acids and serum cholesterol ($P<0{\cdot}05$) and, most notably, triacylglycerol ($P<0{\cdot}001$). Causey *et al.* (2000), also observed a significant reduction in serum triacylglycerol in subjects with moderate hyperlipidaemia, given 18 g/d inulin for 3 weeks.

Clearly data with respect to effects of inulin or oligofructose on blood lipids in humans are inconsistent, with reports of both positive and negative outcomes obtained from recent well designed human studies. There appear to be no obvious differences in the type of oligosaccharide, the dosages employed and duration of treatment, between negative and positive studies (Tables 1 and 2). Positive outcomes have tended to be observed more frequently in those studies conducted in subjects with moderate hyperlipidaemia.

Mechanism of lipid lowering in response to FOS and inulin in humans

Animal studies provide strong evidence that inulin and oligofructose inhibit secretion of TAG-rich VLDL particles via inhibition of *de novo* fatty acid synthesis. If this mechanism is also proposed to be responsible for reduction in blood lipids in humans in response to inulin or oligofructose, then this may explain why the findings are much less clear cut in human than animal studies. As discussed elsewhere (Parks, 2002), high levels of fat present in most human diets mean that rates of hepatic *de novo* fatty acid synthesis are extremely low, since exogenous dietary fatty acids provide all the required substrate for hepatic triacylglycerol synthesis (Aarsland *et al.* 1996).

Although there is some evidence to suggest that inulin and oligofructose may also inhibit the esterification step of fatty acids into triacylglycerols, this is relatively modest in comparison with the marked inhibition of fatty acid synthetase which characterises the response to inulin and oligofructose in animals. Nevertheless, inhibition at this step could conceivably be responsible for some of the observed effects in humans particularly in subjects with hyperlipidaemia where fatty acid esterification rates may be high. These observations suggest that attempts to address the putative triacylglycerol lowering properties of inulin and oligofructose should use subjects consuming a high background dietary carbohydrate intake. Investigations conducted in subjects with NIDDM or those with a dyslipidaemia characteristic of insulin resistance, such as the atherogenic lipoprotein phenotype, would be of particular value.

Conclusions

Although convincing lipid lowering effects of inulin and oligofructose have been observed in animals, the studies have used relatively high levels, equivalent doses of which could not be used in man because of known adverse gastrointestinal side effects at intake levels greater than 15 g per day. Studies that have investigated effects of inulin and oligofructose in humans remain relatively few in number, although those that have been conducted are well designed and include relatively large numbers of subjects. Future studies which aim to investigate effects of inulin or oligofructose on serum lipids should consider the choice of subjects, the duration of the study and the levels of fat and carbohydrate in the background diet as important variables which may influence outcome. Clearly the effector of the hepatic response to inulin and oligofructose feeding in animals, needs to be identified. Although some data exists to suggest short-chain fatty acid products of bacterial fermentation as putative candidates (Todesco *et al.* 1991; Wolever *et al.* 1995), other possibilities, including gut hormones secreted in response to gut fermentation and short-chain fatty acid production, remain to be fully investigated.

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