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Effects of inulin-type fructans on lipid metabolism in man and in animal models

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Studies in rodents show that inulin and oligofructose can reduce the plasma levels of cholesterol and triacylglycerols (TG). In addition, they can oppose TG accumulation in liver and have favourable effects on hepatic steatosis. The hypotriglyceridaemic effect is due to a reduction in hepatic re-esterification of fatty acids, but mainly in the expression and activity of liver lipogenesis, resulting in lower hepatic secretion rate of TG. This repression of lipogenesis is not observed in adipose tissue. The effect on liver lipogenesis can be explained by reduced insulin/glucose levels or by a selective exposure of the liver to increased amounts of propionic acid produced in the large intestine during fermentation of non-digestible carbohydrates. The decrease in plasma cholesterol could also be due to inhibition of cholesterol synthesis by propionic acid or to modifications in the bile acid metabolism. Studies in man yield more conflicting results with a decrease or no effects on plasma lipid levels, and, when a decrease is observed, more marked effects on TG than on cholesterol and more consistent action of inulin than of oligofructose. Besides the difference in the dose of inulin or oligofructose used, differences in metabolic status could play a role in this discrepancy between man and animals since reduction in plasma TG is observed in man mainly in a situation of increased liver lipogenesis (high-carbohydrate diet, obesity, hypertriglyceridaemia). The effects on plasma cholesterol appear also more marked in hyperlipidaemic subjects than in healthy controls, suggesting that inulin and oligofructose have beneficial effects in these types of subjects.

Lipid: Cholesterol: Triacylglycerols: Fibre: Inulin: Oligofructose

Atherosclerosis is a leading cause of death in industrialised societies. Therefore, a reduction in risk factors for atherosclerosis, such as elevated concentrations of plasma total cholesterol and plasma LDL-cholesterol (Klag *et al.* 1993) and raised concentrations of plasma triacylglycerols (TG; Hokanson & Austin, 1996), is a major goal in public health. Such reductions can be achieved with the use of compounds inhibiting cholesterol synthesis (West of Scotland Coronary Prevention Study Group, 1998) or activating nuclear receptors, such as PPARα (Forcheron *et al.* 2002). These reductions can also be obtained at least in part through dietary advice (Jones, 1997), a less expensive approach that can be used for large cohorts of subjects. Increasing the amount of prebiotics in the diet, such as the inulin-type fructans, is one of these possible dietary approaches since it may help to reduce plasma lipid concentrations (Roberfroid, 1993; Delzenne & Kok, 2001). Studies in animals have consistently shown such lipid-lowering actions. Studies in man have produced more conflicting findings, but several do support the usefulness of inulin and/or oligofructose in reducing plasma lipid levels. This review presents results on lipid metabolism in animal and human subjects and discusses possible mechanisms involved in the action of inulin-type fructans.

Studies in animals

Most of the studies have been performed on rats and have investigated the effects of oligofructose, but some have also been conducted on hamsters (Trautwein *et al.* 1998) or dogs (Flickinger *et al.* 2003) and focused on the effects of inulin (Trautwein *et al.* 1998).

Effects on metabolism of triacylglycerols

Studies conducted on lean rats fed a high-carbohydrate diet supplemented (10 % w/w) with oligofructose have consistently shown a decrease in plasma TG levels (Delzenne *et al.* 1993; Fiordaliso *et al.* 1995; Kok *et al.* 1996*b*), both in the fasted and in the fed states. This decrease is associated with lower concentrations of plasma phospholipids (Delzenne *et al.* 1993) and is mostly due to a decrease in the concentration of plasma VLDL-TG in the post-absorptive state (Fiordaliso *et al.* 1995). This TG-lowering effect of oligofructose has also been observed in rats fed a sucrose or a fructose-enriched diet (Aghelli *et al.* 1998; Busserolles *et al.* 2003) and in rats fed a fibre-free diet (Delzenne & Kok, 1999). Furthermore, oligofructose has been reported to decrease postprandial TG concentrations in rats fed a high-fat diet (Kok *et al.* 1998*b*) and inulin to lower plasma TG in hamsters (Trautwein *et al.* 1998) and dogs (Flickinger *et al.* 2003). Some studies have shown a decrease in the intra-hepatic concentration of TG with oligofructose (Daubioul *et al.* 2002; Busserolles *et al.* 2003), suggesting that the hypotriglyceridaemic action results rather from a decrease in the hepatic synthesis of TG than from a higher clearance of TG-rich lipoprotein. The concentration of plasma NEFA, an important source of fatty acids for liver TG synthesis, was not lowered by oligofructose, suggesting that hepatic uptake of NEFA is not modified (Daubioul *et al.* 2002). There is no evidence for an increased hepatic oxidation

Abbreviations: GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide 1; TG, triacylglycerols.

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of fatty acids since the activity of carnitine–palmitoyl transferase 1, the enzyme controlling the entry of long-chain fatty acyl-CoA in mitochondria for oxidation, is unchanged (Delzenne & Kok, 1999). However, hepatocytes isolated from oligofructose-fed rats have a decreased capacity to esterify palmitate (Kok *et al.* 1996*b*). The main hepatic action of oligofructose appears to be a decreased lipogenic capacity (Kok *et al.* 1996*b*). Actually, oligofructose induces a simultaneous decrease in the hepatic expression and activity of the lipogenic enzymes of acetyl-CoA carboxylase, malic enzyme, ATP citrate lyase and fatty acid synthase (Aghelli *et al.* 1998; Delzenne & Kok, 1999). This effect was specific for the liver since oligofructose induced, on the contrary, a moderate increase in fatty acid synthase activity in white adipose tissue (Aghelli *et al.* 1998). This effect of oligofructose may depend on the metabolic status of the rats as this oligosaccharide was shown to reduce hepatic steatosis without any decrease in the raised plasma TG concentrations in obese, insulin-resistant Zucker rats (Daubioul *et al.* 2000). Such a discrepancy between the effects of oligofructose on hepatic and plasma TG levels was also observed in fructose-fed rats (Kok *et al.* 1996*a*). Moreover, oligofructose induced only a moderate decrease in malic enzyme activity in Zucker rats, without any changes in the activity of other lipogenic enzymes (Daubioul *et al.* 2000). In this model, the decrease in liver TG content could be due to an increased secretion of VLDL-TG, but the mechanism remains unclear. Lastly, the addition of oligofructose to a high-fat diet in rats reduced the postprandial TG levels by 50 % (Kok *et al.* 1998*b*), suggesting that oligofructose could also decrease plasma TG by enhancing TG catabolism.

The principal mechanisms of the hypotriglyceridaemic action of inulin-type fructans in animals thus appear to be a decreased expression and activity of the liver lipogenic pathway. However, the link between fructans ingestion and decreased hepatic lipogenesis is still unclear. Mainly nutrients and hormones control hepatic expression of lipogenic genes, insulin and glucose stimulate the expression of lipogenic genes while glucagon and PUFA inhibit it (Girard *et al.* 1994). These effects are mediated through modifications of the expression and/or the activity of the transcription factors sterol responsive element binding protein 1c (Foufelle & Ferré, 2002), carbohydrate responsive element binding protein (Uyeda *et al.* 2002) and liver X receptor (Joseph *et al.* 2002) – all stimulating the expression of lipogenic genes. At present, there are no data on the possible effect of fructans on these transcription factors. Since glucose and insulin have a major stimulatory role in the control of lipogenesis, a decrease in basal or postprandial glucose and insulin levels by inulin-type fructans could be involved. Surprisingly, these parameters were measured only in some studies. The available data are somewhat contradictory and the effects of inulin-type fructans could be dependent on the physiological (basal or postprandial) or disease (insulin-resistance, diabetes) conditions. Rats given oligofructose (10 % in the diet) for 30 d had a moderate decrease in postprandial glucose and insulin concentrations (Kok *et al.* 1996*b*; Delzenne & Kok, 1999), but there were no modifications of the response to an oral glucose load, or only a decrease in the insulinaemic response (Delzenne & Kok, 1999). Oligofructose induced a moderate decrease in basal glucose level of sucrose-fed rats without modification of the response to oral glucose load (Aghelli *et al.* 1998); insulin was not modified, as in fructose-fed rats (Busserolles *et al.* 2003). The basal values and the response of glucose and insulin to oral glucose load were not modified in obese Zucker rats (Daubioul *et al.* 2000). Oligofructose decreased glucose levels in diabetic (streptozotocin-induced) rats, but this appeared to be linked to some increase in residual insulin secretion. Overall, the modifications of glucose and insulin concentrations during administration of oligofructose in rats are limited and their role in the decreased lipogenic capacity of the liver remains to be established.

Inulin-type fructans may also decrease liver lipogenesis through increased production of SCFA in the large bowel or through the modification of the intestinal production of cytokines or incretins. Fermentation of non-digestible carbohydrates in the colon produces SCFA and oligofructose feeding leads to an increase of the portal concentrations of acetate and, more markedly, of propionate (Delzenne & Daubioul, 2000; Daubioul *et al.* 2002). Acetate is a lipogenic substrate, whereas propionate inhibits lipogenesis in isolated hepatocytes of normal (Wright *et al.* 1990; Demigné *et al.* 1995) and Zucker rats (Daubioul *et al.* 2002). This action of propionate could involve a competition between propionate and acetate for the transporter of acetate into hepatocytes (Delzenne & Williams, 2002). Oligofructose administration in the diet of rats increases the plasma and intestinal concentration of glucose-dependent insulinotropic polypeptide (GIP) and of glucagon-like peptide 1 (GLP-1) in the caecum (Kok *et al.* 1998*a*). These peptides are released by the endocrine cells of the intestine and they enhance postprandial insulin secretion. Their possible role in the hypotriglyceridaemic effect of oligofructose remains to be clarified. GIP stimulates lipoprotein lipase activity in the adipose tissue (Knapper *et al.* 1995) and lowers the plasma TG response to an oral fat load in rats (Ebert *et al.* 1991). In addition, GIP decreases incorporation of labelled C from glucose into lipids *in vitro* and thus, probably, decreases hepatic lipogenesis (Kok *et al.* 1998*a*). However, GIP stimulates lipogenesis in adipose tissue (Oben *et al.* 1991) and reinforces the stimulatory effect of insulin on hepatic lipogenesis (Zanpelas *et al.* 1995). Therefore, its overall effect *in vivo* and its possible implication in the action of oligofructose on liver lipogenesis remain unclear. There are presently no data on the effect of GLP-1 on hepatic lipogenesis. Another possible mechanism of action of oligofructose, which remains to be investigated, could be the modification of intestinal bacterial content and intestinal permeability, a reduction of endotoxaemia and production of cytokines like IL-6 and TNF-α that can both stimulate hepatic lipogenesis (Brass & Vetter, 1994; Lawler *et al.* 1998; Wigg *et al.* 2001).

Effects on cholesterol metabolism

Studies on the effect of inulin and oligofructose on cholesterol in animals produced more conflicting results. The addition of oligofructose to the diet did not decrease plasma cholesterol in lean (Delzenne *et al.* 1993; Kok *et al.* 1996*a*; Aghelli *et al.* 1998) or obese Zucker (Daubioul *et al.* 2000) rats or in dogs (Flickinger *et al.* 2003). In another, more prolonged study, 10 % dietary oligofructose induced a moderate (−15 %) reduction of plasma cholesterol in rats (Fiordaliso *et al.* 1995). Lastly, oligofructose prevented the hypercholesterolaemic effect of a high-fat diet in rats. The effects of inulin appear more consistent. Although inulin had no significant effect in dogs (Flickinger *et al.* 2003), it had a significant hypocholesterolaemic effect in rats (Levrat *et al.* 1994) and a marked effect in hamsters (Trautwein *et al.* 1998; a more appropriate model because of better similarities with human cholesterol metabolism). The reduction in cholesterol level was limited to esterified cholesterol (Fiordaliso *et al.* 1995)

and to the VLDL fraction without changes in LDL- and HDL-cholesterol (Fiordaliso *et al.* 1995; Trautwein *et al.* 1998).

Several mechanisms have been proposed to explain the hypocholesterolaemic effect. The limitation of the decrease in plasma cholesterol to the VLDL fraction suggests that the decreased synthesis and secretion of VLDL has a major role. It has been proposed that propionate, whose intestinal production is increased by inulin-type fructans administration, could inhibit hepatic cholesterol synthesis (Demigné *et al.* 1995), but other studies did not show convincing evidence for this effect (Nishina & Freeland, 1990; Levrat *et al.* 1994). Intestinal absorption of cholesterol does not seem to be impaired (Trautwein *et al.* 1998). Although inulin-type fructans do not share all the properties of other viscous fibres such as psyllium (Schneeman, 1999; Fernandez, 2001), they may increase faecal bile acid excretion (Levrat *et al.* 1994; Trautwein *et al.* 1998). They could, therefore, stimulate liver synthesis of bile acids from cholesterol and this could contribute to their cholesterol-lowering action.

Studies in man

While data obtained for animals showed convincing lipid-lowering properties of inulin-type fructans, studies conducted in man are more conflicting. Tables 1 and 2 summarise the results obtained for control subjects (Table 1) and for type 2 diabetic or hyperlipidaemic patients (Table 2).

Of the five studies conducted on healthy subjects, the two investigating the effect of oligofructose found no modifications of plasma lipids, glucose or insulin concentrations (Luo *et al.* 1996; Van Dokum *et al.* 1999). Inulin, investigated in four studies, had no effect in two (Pedersen *et al.* 1997; Van Dokum *et al.* 1999) and induced a decrease in TG in one (Letexier *et al.* 2003*a*), while both TG and cholesterol were decreased in the last study (Brighenti *et al.* 1999). Luo *et al.* (1996) investigated the effect of oligofructose (20 g/d in cookies) on twelve men in a randomised crossover design with a 4-week treatment period. There was a small decrease in hepatic glucose production, but no changes in glucose, insulin, TG or cholesterol concentrations. Pedersen *et al.* (1997) observed no effect on plasma lipids in sixty-four young women ingesting inulin daily (14 g daily for 4 weeks in a randomised, double-blind, crossover design). Van Dokum *et al.* (1999) investigated the effects of inulin and oligofructose (15 g daily for 3 weeks in a randomised, double-blind design) on twelve healthy men and found no modifications of glucose, insulin or plasma lipid levels by either of the fructans used. In contrast, Brighenti *et al.* (1999) found a marked reduction in the plasma TG levels and a moderate decrease in plasma cholesterol in twelve men consuming 9 g inulin/d. Lastly, Letexier *et al.* (2003*a*) observed a 16 % decrease in plasma TG in eight control subjects ingesting 10 g inulin/d (randomised, double-blind, crossover design); in this last study, all the subjects consumed a carefully controlled isoenergetic, but moderately high, carbohydrate (55 % of energy intake) diet.

More promising results were obtained in type 2 diabetic patients and mostly in hyperlipidaemic subjects. Yamashita *et al.* (1984) investigated the effect of a 14 d administration of oligofructose (8 g/d) on eighteen patients with uncontrolled diabetes. They observed a small decrease in post-absorptive glucose (8 %) and total cholesterol (6 %) that was due to a reduction in LDL-cholesterol. HDL-cholesterol, TG and NEFA were not modified.

Table 1. Summary of the effects of inulin and oligofructose on healthy human subjects

	Subjects	Fructans (g)	Design	Lipids	Glucose, IRI
Luo *et al.* (1996)	12 men	OFS, 20	4 weeks, DB, CO	NS	NS
Pedersen *et al.* (1997)	66 women	Inulin, 14	4 weeks, DB, CO	NS	nd
Brighenti *et al.* (1999)	12 men	Inulin, 9	4 weeks, parallel	TG −27% Chol −7%	NS
Van Dokum *et al.* (1999)	12 men	Inulin, 15	3 weeks, DB	NS	NS
		OFS, 15	3 weeks, DB	NS	NS
Letexier *et al.* (2003*a*)	4 men, 4 women	Inulin-HP, 10	HCHO diet 6 weeks, DB, CO	TG −16 %	NS

IRI, insulin resistance index; OFS, oligofructose; inulin-HP, high-molecular-weight inulin; DB, double-blind; CO, crossover; HCHO, high carbohydrate; TG, triacylglycerols; chol, cholesterol; nd, not determined.

Table 2. Summary of the effects of inulin and oligofructose on diabetic and hyperlipidaemic human subjects

	Subjects	Fructans (g)	Design	Lipids	Glucose, IRI
Yamashita *et al.* (1984)	18 NIDDM	OFS, 8	2 weeks, DB, parallel	Chol −6 %	Glucose
Luo *et al.* (2000)	10 NIDDM	OFS, 20	4 weeks, DB, CO	NS	NS
Alles *et al.* (1999)	20 NIDDM	OFS, 15	3 weeks, SB, CO	NS	NS
Hidaka *et al.* (1991)	37 HC	OFS, 20	5 weeks, DB, parallel	Chol −8 %	NS
Davidson *et al.* (1998)	21 HC	Inulin, 18	6 weeks, DB, CO	Chol −9 %	nd
Jackson *et al.* (1999)	54 HC, HTG	Inulin, 10	8 weeks, DB, parallel	TG −19 %	IRI
Causey *et al.* (2000)	12 HTG	Inulin, 20	3 weeks, DB, CO	TG −14 %	NS
Balcazar *et al.* (2003)	12 HC, HTG	Inulin, 7	4 weeks, DB, parallel	Chol −20 % TG −27 %	NS

IRI, insulin resistance index; NIDDM, non-insulin dependent diabetes mellitus; HC, hypercholesterolaemic; HTG, hypertriglycideraemic; OFS, oligofructose; DB, double-blind; CO, crossover; SB, single-blind; chol, cholesterol; TG, triacylglycerols; nd, not determined.

No precise data on diet were given, making it difficult to conclude whether these moderate decreases in glucose and cholesterol were due to changes in diet or due to the addition of oligofructose. In contrast, two more recent studies (Alles *et al.* 1999; Luo *et al.* 2000) found no significant effect on either glucose or lipid (TG, total, LDL- and HDL-cholesterol, NEFA) concentrations, despite higher doses of oligofructose (15 and 20 g, crossover, placebo-controlled studies). The most encouraging results were observed in hyperlipidaemic subjects. The only study investigating the effect of oligofructose in such subjects found a moderate decrease of total plasma cholesterol (Hidaka *et al.* 1991). Four studies investigated the effect of inulin in subjects with moderate hypercholesterolaemia (Davidson *et al.* 1998; Davidson & Maki, 1999) or with raised TG and cholesterol concentrations (Jackson *et al.* 1999; Causey *et al.* 2000; Balcazar-Munoz *et al.* 2003). Balcazar-Munoz *et al.* (2003) compared the effect of inulin (7 g/d) and placebo (randomised, double-blind study) on twelve obese, hyperlipidaemic subjects. Inulin decreased both TG (−27 %) and total cholesterol (−20 %), with a decrease in both VLDL- and LDL-cholesterol. Insulin sensitivity was not modified. The other studies found, despite the use of higher inulin doses (10–20 g/d), significant decreases only in cholesterol (Davidson *et al.* 1998; Davidson & Maki, 1999) or TG (Jackson *et al.* 1999; Causey *et al.* 2000). In the study of Jackson *et al.* (1999), the decrease in TG was all the more important since the initial value was high; in addition, basal insulin levels were also decreased and this fall in insulinaemia may have played a role in the decrease in TG concentration.

Comparisons between animal and human studies

Studies in animals show consistent effects of inulin-type fructans on plasma TG levels and, to a lesser degree, on cholesterol concentrations, whereas more conflicting results are observed in man. Several explanations for this discrepancy between human and animal studies can be proposed. The first, and simplest one, is the use of much higher doses of oligofructose or inulin in animal studies. The use of comparable doses in man is precluded by the risk of uncomfortable gastrointestinal side-effects. However, in human studies, significant results were observed with low doses (7–10 g in Brighenti *et al.* 1999; Balcazar-Munoz *et al.* 2003; Letexier *et al.* 2003*a*), while higher doses (15–20 g) induced no or less important effects (Luo *et al.* 1996; Pedersen *et al.* 1997; Van Dokum *et al.* 1999). Another explanation relates to the main mechanism proposed for the hypotriglyceridaemic effect of inulin-type fructans in animals: inhibition of hepatic *de novo* lipogenesis. In man, hepatic *de novo* lipogenic rate is low and contributes only a few percent to the TG secreted by the liver (Diraison & Beylot, 1998). Therefore, only modest effects of the inhibition of hepatic lipogenesis can be expected unless its activity is previously raised by nutritional or pathological factors. Indeed, a significant hypotriglyceridaemic effect of inulin was observed in subjects receiving a controlled, moderately high, carbohydrate diet, a situation known to stimulate hepatic lipogenesis (Hudgins *et al.* 1996; Letexier *et al.* 2003*b*), and the decrease in TG was related, as during animal studies, to a reduction in hepatic lipogenesis (Letexier *et al.* 2003*a*). This could also explain the more consistent effect of inulin in human subjects with obesity and hypertriglyceridaemia than in control, healthy subjects, since obese and hypertriglyceridaemic subjects have also an enhanced hepatic lipogenic rate (Diraison *et al.* 2002; Forcheron *et al.* 2002). Lastly, difficulties in controlling nutrient intake, and, therefore, variations in this intake during the course of the studies, could also contribute to the relative discrepancy between human and animal studies. The precise mechanism of the cholesterol-lowering effect of inulin-type fructans in man remains elusive, as it does for studies in animals. The finding of a simultaneous decrease in VLDL-cholesterol and TG (Balcazar-Munoz *et al.* 2003) suggests that a decrease in the secretion of VLDL and, therefore, of cholesterol by the liver could contribute. A decrease in hepatic cholesterol synthesis may participate in this reduction of cholesterol secretion by the liver since propionate has been shown to induce a moderate reduction in the incorporation of labelled acetate into cholesterol (Wolever *et al.* 1995). A decrease in intestinal cholesterol absorption or an increase in bile acids synthesis from cholesterol secondary to a reduced reabsorption of bile acids seems unlikely since neither faecal bile acids excretion (Ellegärd *et al.* 1997; Brighenti *et al.* 1999) nor cholesterol excretion (Ellegärd *et al.* 1997) was modified in man by inulin.

Conclusions

It is clear that dietary inulin-type fructans have TG- and cholesterol-lowering effects in rodents. They may also have a protective effect on the accumulation of TG in the liver and the development of steatosis in animals. The results in man are more conflicting, especially in healthy subjects. Fortunately, positive results are observed in most studies conducted on subjects with raised lipid levels. In these subjects, inulin appears more effective than oligofructose; the effect on TG levels is larger than for cholesterol and, when present, these hypotriglyceridaemic and hypocholesterolaemic effects are comparable from one study to another. A decrease in liver *de novo* lipogenesis is probably the main mechanism responsible for the decrease in plasma TG levels, both in man and in animals, whereas the mechanism of the hypocholesterolaemic action remains uncertain. Further mechanistic studies are needed to resolve this. Further studies should also aim at determining whether inulin-type fructans may indeed protect against liver steatosis, and possibly against excess deposit of lipids in other tissues. Lastly, it is important to determine whether their effects are additive or not with other dietary (modifications of cholesterol amount or of the ratio of saturated to unsaturated fatty acids in the diet) or pharmacological intervention.

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