

Dietary Fructans and Serum Triacylglycerols: A Meta-Analysis of Randomized Controlled Trials¹⁻³

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Abstract

Convincing evidence indicates that the intake of inulin-type fructans, inulin and oligofructose, has beneficial effects on blood lipid changes in animals, although data in humans have been considered contradictory. We conducted a meta-analysis of available literature to quantify the effects in humans of dietary inulin-type fructans on serum triacylglycerols. Fifteen eligible randomized, controlled trials published from 1995 to 2005, for a total of 16 comparisons, were identified from the PubMed (National Library of Medicine, Bethesda, MD) and SCOPUS (Elsevier B.V., Amsterdam, NL) databases. Standardized mean effect sizes were calculated for net changes in serum triacylglycerol concentrations using random-effect model. The intake of inulin-type fructans was associated with significant decreases in serum triacylglycerols by 0.17 mmol/L (95% CI -0.33, -0.01; $Z = 2.12$, $P = 0.04$) or 7.5%. Given the limited number of studies, no specific effects for gender, amount fed, duration of the study, background diet, overweight, hyperlipidemia, or diabetes were further formally investigated, but, from the test for heterogeneity [$\chi^2 = 13.34$, $df = 15$, ($P = 0.55$), $I^2 = 0\%$], it appears that the effect of inulin-type fructans on circulating triacylglycerols is consistent across conditions. In conclusion, dietary inulin-type fructans significantly reduced serum triacylglycerols. The mechanisms, possibly related to colonic fermentation and/or incretin release from the distal gut, warrant further studies. *J. Nutr.* 137: 2552S–2556S, 2007.

Introduction

Hypertriglyceridemia, especially when linked to other metabolic abnormalities, is an emerging target for coronary heart disease (CHD) prevention. The lipid triad, a highly atherogenic combined dyslipidemia characterized by low levels of HDL, elevated triacylglycerols and elevated small, dense LDL particles, represents the most important modifiable risk factor for CHD (1). Some triacylglycerol-rich lipoproteins, such as chylomicrons and large VLDL, are probably not able to cross the endothelial barrier and

enter the arterial intima, whereas small VLDL and intermediate-density lipoproteins are much more atherogenic (2).

Therefore, strategies aimed to reduce the levels of triacylglycerols are highly recommended, especially in overweight insulin-resistant individuals where hypertriglyceridemia is linked to raised small VLDL and IDL and low HDL and represents a distinctive component of the metabolic syndrome.

Diet is considered the cornerstone in the treatment of elevated triacylglycerol levels; moderation in alcohol consumption and reduction of carbohydrate in general, and sucrose in particular, are the first recommendations traditionally given to prevent and treat hypertriglyceridemia (3). As an adjuvant to a healthy diet, back in 1993 (4) the inulin-type fructans i.e., inulin and oligofructose, have been proposed as functional food ingredients able to reduce plasma triacylglycerols, and indeed, a consistent stream of animal studies has confirmed this hypothesis (5). However, the results of studies in humans have been considered less clear-cut, with studies on this argument unable either to confirm or rule out the effect of inulin-type fructans in lowering triacylglycerols to a significant extent (6–9). The aim of this work is to conduct a meta-analysis of available literature to quantify the effects in humans of dietary inulin and oligofructose on serum triacylglycerols.

Methods

Identification and selection of studies. Randomized controlled trials of the effects of dietary inulin-type fructans i.e., inulin and oligofructose, on serum lipid concentrations in humans published in the last 10 y (from January 1996 to June 2006) were searched in the scientific literature by

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³ In these proceedings, the term inulin-type fructan shall be used as a generic term to cover all β -(2 \leftarrow 1) linear fructans. In any other circumstances that justify the identification of the oligomers vs. the polymers, the terms oligofructose and/or inulin or eventually long-chain or high-molecular-weight inulin will be used, respectively. Even though the oligomers obtained by partial hydrolysis of inulin or by enzymatic synthesis have a slightly different $DP_{n,w}$ (4 and 3.6, respectively), the term oligofructose shall be used to identify both. Synergy will be used to identify the 30/70 mixture (wt:wt) of oligofructose and inulin HP otherwise named oligofructose-enriched inulin.

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consulting the PubMed (National Library of Medicine, Bethesda, MD) and SCOPUS (Elsevier B.V., Amsterdam, NL) databases. The words fructan, inulin, oligofructose, fructo(-)oligosaccharide, lipid, triglyceride, and triacylglycerol in either title, abstract, or keywords of clinical trials published in English, Italian, Spanish, or French languages were used as search terms. Four reviews (6,7,9,10) on the specific topic were also examined for cited references. From the 40 resulting references, articles were identified that met the following criteria: 1) they referred to human studies; 2) they specified the type and the amount of dietary inulin-type fructans employed; 3) they were placebo controlled with either a randomized crossover, parallel, or sequential design; and 4) they provided measures of serum triacylglycerol concentrations that included either standard deviation, standard error of the mean, confidence intervals, or exact *P*-values for *t* test or *F*-values for ANOVA, so that changes and standard deviation estimates could be calculated. Studies were excluded if the amount of inulin-type fructans and the lipid values at outcome were not provided or if there was no control group. After exclusion of articles that did not meet the inclusion criteria, a meta-analysis of 15 eligible articles (11–25) was performed. One study (18) reported results of a trial in which multiple comparisons were made on the effects of 3 different prebiotics (oligofructose, inulin, and GOS) with crossover assignment of diets according to a Latin square design. In this case, the effects observed for oligofructose and inulin were considered separately as 2 independent studies (van Dokkum 1 and van Dokkum 2).

Meta-analysis. The characteristics of each trial and selected summary results of the study were extracted for analysis and tabulated using REVMAN software version 4.1 (Cochrane Collaboration, Oxford, UK). The same software was used for all other calculations. Data provided in non-SI format (i.e., mg/100 mL) were transformed to mmol/L by multiplying by 0.0113, according to laboratory standard conversion factor. The estimate of the principal effect was defined as the mean difference (net change in mmol/L) between the change in triacylglycerol concentrations among the subjects consuming the test diet (containing either inulin or oligofructose) calculated as the final value minus initial value, and that among the subjects consuming the control diet.

For the computation of pooled effect size, standardized mean difference was used. Because no study reported raw data, the variance for each study was calculated based on the reported SDs for each measure for the change during the test diet and the change during the control diet.

In 3 cases (18,21,23) where initial triacylglycerols values were not provided, data after the control condition were used as basal values. In

the case of studies reporting data for multiple time points, only endpoints for the longest duration were used.

Estimates of the average effect of inulin-type fructans on lipid values and 95% CIs were initially calculated using both fixed-effect and random-effect models. Even though the test for heterogeneity was not significant ($P = 0.55$), only the results of the more conservative random effect model are presented because the assumption of heterogeneity implied by the use of random-effects models is plausible in light of differences in amounts of active substance, study durations, initial lipid concentrations, and the presence of other covariates (26). Finally, a funnel plot of the SEs of the studies against their corresponding effect size was drawn to identify potential publication bias.

Results and Discussion

Characteristics of the studies. Selected characteristics of the 15 studies that met the selection criteria, for a total of 16 comparisons, are shown in Table 1. Overall, 290 subjects for each condition were included in the meta-analysis. Nine studies focused on men, 1 on women, and the remaining studies included both sexes. Subjects were either hypercholesterolemic or hypertriglyceridemic at baseline in 4 studies (14,19,21,22,24), type II diabetics in 2 studies (17,20), nonalcoholic fatty liver disease (NAFLD) patients in 1 study (25), and apparently healthy individuals in the remaining 9 studies. Eleven of 16 studies used a crossover design; 2 (19,22) used a parallel, and 3 (15,16,24) a sequential design. The test substance was oligofructose in 6 studies (11,13,17,20,24,25) and inulin of different chain lengths in 8 studies (12,14–16,19,21–23); 1 study (18) used both oligofructose and inulin in 2 separate study arms. The average amount of active substance fed was 14 g/d for oligofructose (range 8–20) and 14.2 g/d for inulin (range 4–32). In 1 study inulin-type fructans were fed together with probiotic microorganisms (13). The test substance was administered either as sweetener or powder consumed alone or added to drinks, or as an ingredient of spreads (12,14), biscuits (11), breakfast cereals (16), orange juice (18), or fermented milk (13,15) products. The trials varied in length from 21 to 64 d, with a median duration of 28 d, a time considered sufficient to observe dietary-induced effects on blood lipids (27).

TABLE 1 Characteristics of the 15 studies, including 16 comparisons

Study	Year	Subjects, <i>n</i> (parallel arms)	Gender	Design	Treatment	Amount	Vehicle	Study length	Status
Luo	1996	12	Males	CT	Oligofructose	20	Biscuit	28	Norm.
Pedersen	1997	66	Females	CT	Inulin	14	Spread	28	Norm.
Davidson	1998	21	Males/Females	CT	Inulin	18	Chocolate, spreads, sweeteners	42	Mod. hyperchol
Schaafsma	1998	30	Males	CT	Oligofructose	9.4	Fermented milk	21	Norm.
Alles	1999	20	Males/Females	CT	Oligofructose	15	Sweetener	21	NIDDM
Brighenti	1999	12	Males	SEQ	Inulin	9	Breakfast cereals	28	Norm.
Jackson	1999	54 (27/27)	Males	PA	Inulin	10	Sweetener	56	Mod. hyper-TG
Kruse	1999	8	Males/Females	SEQ	Inulin	22–34	Added to yogurt	64	Norm.
van Dokkum 1	1999	12	Males	LS	Oligofructose	15	Sweetener (orange juice)	21	Norm.
van Dokkum 2	1999	12	Males	LS	Inulin	15	Sweetener (orange juice)	21	Norm.
Causey	2000	12	Males	CT	Inulin	20	Ice cream	21	Mod. hyper-TG
Luo 2	2000	10	Males/Females	CT	Oligofructose	20	Sweetener	28	NIDDM
Balcazar-Munoz	2003	12 (6/6)	Males	PA	Inulin	4	Sweetener	28	Mod. hyper-TG
Letexier	2003	8	Males/Females	CT	Inulin	10	Sweetener	21	Norm.
Giacco	2004	27	Males/Females	SEQ	Oligofructose	10.6	Sweetener	60	Mod. hyperchol
Daubioul	2005	7	Males	CT	Oligofructose	8	Sweetener	56	NAFLD/NASH

Design: CT = crossover; SEQ = sequential; PA = parallel; LS = crossover with more than 2 treatments, Latin square assignment. Status: Norm: normals; Mod. hyperchol = moderately hypercholesterolemic; Mod. hyper-TG = moderately hypertriglyceridemic; NIDDM = noninsulin dependent diabetes mellitus; NAFLD/NASH = nonalcoholic fatty liver disease, nonalcoholic steatohepatitis.

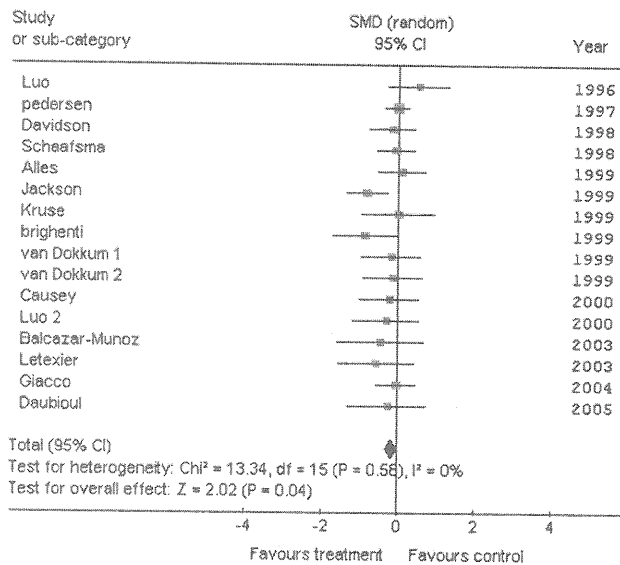


FIGURE 1 Net change (and 95% CI) in triacylglycerols associated with consumption of inulin-type fructans. SMD, standardized mean difference; random, random-effect model. The horizontal lines denote the 95% CIs. The diamond represents the overall summary estimate.

Changes in serum lipid concentrations. For the 16 comparisons, including only the longest intervention period, triacylglycerols decreased in the group containing inulin-type fructans compared with the corresponding control group in 13 (81%) of the comparisons (Fig. 1). Study data are summarized in Table 2. Overall, the intervention with inulin-type fructans significantly decreased serum triacylglycerols by -0.17 mmol/L (95% CI: -0.33 , -0.01 ; $Z = 2.02$, $P < 0.04$), or 7.5%. The funnel plot of the effects on total cholesterol by SE in 16 comparisons of inulin-type fructans indicated no significant publication bias (data not shown).

TABLE 2 Changes in triacylglycerols compared with initial values, standardized weights and effect size (95% CI) associated with consumption of fructans

Study	Year	Δ Treatment			Δ Control			Variance	Weight	Effect size	95% CI start	95% CI end	SE
		n	Mean	SD	n	Mean	SD						
Luo	1996	12	0.10	0.42	12	-0.08	0.22	0.1734	4.05	0.5184	-0.2977	1.3345	0.4164
Pedersen	1997	66	0.02	0.35	66	0.03	0.37	0.0303	23.16	-0.0276	-0.3688	0.3136	0.1741
Davidson	1998	21	-0.05	0.51	21	0.05	0.70	0.0956	7.34	-0.1602	-0.7661	0.4457	0.3092
Schaafsma	1998	30	0.08	0.75	30	0.13	0.72	0.0667	10.52	-0.0671	-0.5733	0.4391	0.2583
Alles	1999	20	-0.25	1.36	20	-0.37	1.20	0.1001	7.01	0.0917	-0.5284	0.7119	0.3164
Brighenti	1999	12	-0.23	0.24	12	0.00	0.27	0.1855	3.78	-0.8694	-1.7135	-0.0252	0.4307
Jackson	1999	27	-0.17	0.37	27	0.19	0.49	0.0807	8.69	-0.8172	-1.3741	-0.2602	0.2842
Kruse	1999	8	0.20	0.28	8	0.20	0.24	0.2500	2.81	0.0000	-0.9800	0.9800	0.5000
van Dokkum 1	1999	12	-0.11	0.58	12	0.00	0.65	0.1674	4.19	-0.1724	-0.9743	0.6295	0.4092
van Dokkum 2	1999	12	-0.09	0.61	12	0.00	0.65	0.1671	4.20	-0.1379	-0.9391	0.6634	0.4088
Causey	2000	12	-0.45	1.93	12	0.00	2.10	0.1678	4.18	-0.2154	-1.0184	0.5875	0.4097
Luo 2	2000	10	0.16	0.47	10	0.29	0.35	0.2028	3.46	-0.3005	-1.1831	0.5822	0.4503
Balcazar-Munoz	2003	6	-0.73	0.68	6	-0.40	0.69	0.1721	2.03	-0.4447	-1.5969	0.7075	0.5879
Letexier	2003	8	-0.15	0.24	8	0.00	0.26	0.2633	2.67	-0.5668	-1.5726	0.4389	0.5131
Giacco	2004	27	1.53	0.71	27	1.56	0.53	0.0741	9.47	-0.0472	-0.5807	0.4863	0.2722
Daubioul	2005	7	-0.35	0.56	7	-0.18	0.62	0.2893	2.43	-0.2694	-1.3236	0.7848	0.5379
Combined	—	290	—	—	—	—	—	—	100	-0.1693	-0.3335	-0.0051	0.0838

Discussion

This is the first quantitative review of randomized clinical trials yielding information on the effect of fructans on serum triacylglycerols. The meta-analysis showed that the intake of inulin-type fructans, i.e., inulin and oligofructose, was associated with a significant decrease (-0.17 mmol/L) in serum triacylglycerol concentrations. These findings are based on data of 15 individual published reports, in which 81% of trials showed an association between intake of inulin-type fructans and decrease in lipid concentrations, although significantly in only 5 studies (16,19,21–23). The substantial homogeneity among studies suggests that changes associated with ingestion of inulin-type fructans do not depend on the condition of the subject (i.e., the initial lipid status) or on the type of inulin-type fructan fed, and an effect could potentially be seen across conditions in the majority of the subjects consuming fructans in their diet. Regarding the clinical significance of this finding, the extent of reduction in triacylglycerols ($-7.5%$) is relatively small when compared with the effect ($\sim -27%$) of both sustained weight loss (28) and fish oil consumption (29), not to mention comparisons with drug treatments specifically aimed at lowering lipids or treating insulin resistance. However, the reduction in serum triacylglycerols is well comparable with other dietary and behavioral strategies, such as the result ($-8.3%$) of the treatment with moderate-carbohydrate, high-fiber vs. moderate-carbohydrate, low-fiber diets in diabetic patients (30), the result ($-7.3%$) of the use of soy protein containing isoflavones (31), or the effect ($-5%$ and $-9%$) observed after sustained aerobic exercise in women (32) and men (33), respectively.

The biological mechanisms by which inulin-type fructans are able to reduce serum triacylglycerols in humans remain obscure, even though studies in different animal models have clearly shown that a down-regulation of hepatic lipogenesis could play a role (5,6). Because inulin-type fructans are not absorbed, and, at least in humans, they have no effect on postprandial blood glucose (16,21,24) but can inconsistently either raise (21) or lower (24) insulin response, it is likely that their effects are mediated by events related to colonic fermentation.

Vogt et al. (34) reported that 25 g/d of the fermentable sugars lactulose and L-rhamnose reduce serum triacylglycerols and their rates of synthesis. Similarly, Letexier et al. (23) reported a reduction in hepatic lipogenesis together with a reduction in serum triacylglycerols in healthy subjects fed 10 g/d of inulin. A SCFA of colonic origin, and specifically of propionic acid, in the inhibition or down-regulation of liver lipogenic pathways has been suggested (35) but is still speculative. A second mechanism could be related to altered secretion of gastrointestinal hormones induced by the presence and/or fermentation of nutrients and fibers in the distal gut. Of some interest may be the finding that surgically induced malabsorption has a major impact on altered lipid metabolism that is not completely explained by a normalization in body weight. As an example, Roux-en-Y gastric bypass for the treatment of morbid obesity is effective in reversing NAFLD and in normalizing VLDL-TG secretion rates in obese patients despite a final BMI still in the range of morbid obesity (41 ± 5) (36). Moreover, biliopancreatic diversion, a procedure that induces severe malabsorption, is able to reverse insulin resistance and normalize altered blood lipids much faster than gastric bypass and long before normalization of body weight (37). Bariatric surgery is also able to normalize the low levels of glucagon-like peptide 1 (GLP-1) that can be seen in obese patients compared with normal-weight controls (38). In addition to the effect of weight loss, this might suggest a role of more distal absorption and/or of increased malabsorption of nutrients to the colon in regulating GLP-1 and other gastrointestinal peptides.

Recently, it has been shown that infusion of GLP-1 during the meal completely abolishes the rise in postprandial triglycerideemia in healthy volunteers (39).

Inulin and oligofructose increase colonic and portal GLP-1 levels in rats (40) and mice (41), and the addition of sodium propionate and fat to a pasta meal increases postprandial GLP-1 levels in normal volunteers (42). However, the addition of the less fermentable psyllium (42) and cereal (43,44) fibers to a meal does not modify postprandial GLP-1 levels, thus suggesting that the rate of fermentability of undigested carbohydrate and/or their SCFA profile could play a major role.

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