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Active Food Scientific Monitor

Interview
with Professor
Dr. David Jenkins

In this issue we present an interview with Prof. Dr. David Jenkins of the Department of Nutrition from the University of Toronto, Canada.

Antiquities and classical art

Professor David J.A. Jenkins is director of the Risk Factor Modification Center, St. Michael's Hospital, and a professor in both the Departments of Medicine and Nutritional Sciences at the Faculty of Medicine, University of Toronto, as well as a staff physician in the Division of Endocrinology and Metabolism at St. Michael's Hospital. He was educated at Oxford University where he held a joint appointment in the Department of the Regius Professor of Medicine at the Radcliffe Infirmary and as a faculty member of the University Laboratory of Physiology.
David Jenkins is also an amateur and collector of antiquities and classical art from the Greek and Roman Period. "Although I travel a lot in Greece and Italy, I must admit that most of my collection comes from New York."

Inulin and oligofructose have attracted a significant amount of attention as non-digestible carbohydrates with prebiotic properties through their ability to modify the colonic microflora. Their low glycemic index and their effects on lipid metabolism put them at the forefront of research for the reduction of cardiovascular disease and diabetes risk. Fibres in general, combined with plant proteins and with plant sterols in the diet, may be able to form a powerful combination for risk management of heart disease and diabetes.

The role of inulin, oligofructose and dietary fibre in the management of diabetes

What is the role of dietary fibre in controlling the risk factors of diabetes?
The addition of various dietary fibres and non-absorbable carbohydrates to the diet of diabetics may improve their health condition in several ways. One reason is that they slow the rate of nutrient absorption, which spares the pancreas from peak insulin secretions and allows a gradual rise and decline of blood sugar levels. Dietary fibres also have been associated with increased suppression of free-fatty acid formation, which allows carbohydrate to be utilised more effectively by the tissues. The effects of dietary fibre on colonic function appears to

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P R E F A C E

by Dr. Anne Franck

Active Food
Scientific Monitor

Since the prebiotic concept was introduced to the food industry in the early 1990s, the number of scientific studies carried out on Raftiline® (inulin) and Raftilose® (oligofructose) has been increasing annually, providing insight into the confirmed and potential nutritional benefits of these ingredients on health. Research teams from around the world are reporting interesting new results on a regular basis. The science supporting the nutritional benefits of inulin and oligofructose has come a long way in recent years. And there is much to be excited about, including the potential for positive effects of increased inulin and oligofructose consumption on intestinal health, mineral absorption and well-being.

For example, the EU-sponsored SYNCAN project is looking at the potential effects of synbiotics, which are combinations of probiotics and prebiotics, on the reduction of risk of colon cancer, both in animal models and in human volunteers. The project, co-ordinated by ORAFTI, has been running since 2000.

Immune response modulation is another area about which there is still much to learn, but research in animal models has already shown positive effects of prebiotics.

Of particular interest since a few years is the effect of Raftilose®Synergy1 on mineral (calcium and magnesium) absorption and bone metabolism in adolescents and post-menopausal women.

Further research highlights at the moment include the effect of inulin and oligofructose on the secretion of specific gut hormones, as well as the benefits of prebiotic ingredients on gut flora modulation and resistance to gastro-intestinal infections and diseases.

So, as you can see, there is much interesting work going on at this time.

The 4th ORAFTI Research Conference will provide an important forum for scientists, researchers and representatives from the food industry to share and discuss the latest science on the nutritional and health benefits of Raftiline® and Raftilose®. The conference entitled "Inulin and Oligofructose - FeelGood Factors for Health and Well-being" is to take place in Paris on February 12-13, 2004. Twenty-four key scientific experts will present the progress of all of the latest research looking at inulin and oligofructose and their benefits to health and well-being. There will also be the opportunity for discussion and exchanging ideas. So, we sincerely hope to see you there.

REMINDER

Paris
February 12-13, 2004

The 4th ORAFTI Research Conference

"Inulin and Oligofructose - FeelGood Factors for Health and Well-being"

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The role of inulin, oligofructose and dietary fibre in the management of diabetes

result in altered cholesterol metabolism. As diabetics are obviously at risk for heart disease, anything that could be done to improve lipid metabolism is a major health benefit.

The effects of dietary fibre on glucose metabolism are probably mediated by their action on insulin secretion and lipid metabolism.

It has been shown that the inclusion of dietary fibre in a meal of both normal and diabetic volunteers attenuates the postprandial glycemic and insulinemic responses and favorably influences plasma lipid levels. In the longer term, this reduces urinary glucose excretion and improves diabetes control. Furthermore, dietary fibre increases bile acid output in the faeces and changes the bile acid composition, which may have additional beneficial effects on cholesterol metabolism in terms of reducing LDL-cholesterol.

In the context of high-fibre/high-carbohydrate diets, these findings have had a major impact on international recommendations for the dietary management of diabetes. The mechanism of action appears in part to be due to the fibre slowing nutrient absorption rather than increasing carbohydrate excretion via the colon.

No single fibre is likely to have all of these health effects combined. Some may, but that is very rare. The sticky or viscous types of soluble fibre tend to be the ones that slow nutrient absorption in the small intestine. Consequently postprandial Glucose-dependent Insulinotropic Peptide (GIP) and insulin levels are reduced. The fermentable fibres on the other hand may change the composition of the colonic microflora. This enhances glucose utilisation and exerts related health effects. Thus, in the diet there is a role for each type of dietary fibre and they complement each other.

What may be the potential benefit of inulin and/or oligofructose in the diet of diabetic patients?

Inulin and oligofructose could add benefit to the diet of diabetics in different ways.

The short-chain fructans (oligofructose) can provide bulk and sweetness to food without actually causing a significant postprandial change in blood glucose level and insulin requirement. Secondly, inulin and oligofructose alter the colonic microflora which increases short-chain fatty acid production. Intestinal short-chain fatty acids show health benefits on immune function, as well as on lipid and cholesterol metabolism, which provides a definite direct benefit for diabetics. Probably related to their effect on immune function and cholesterol metabolism, fructans also seem to have important anticancer properties. This may be particularly important for diabetic patients who are known to be vulnerable to a number of cancers, especially colorectal cancer. It can be stated that fructans are well suited for diabetics, not only because they do not challenge the blood glucose and insulin regulation, but also because their additional health benefits are of particular use for this target population.

In your research, you look at the health effects obtained when combining different types of fibre with other food ingredients?

Yes, indeed. We are particularly interested in inulin and oligofructose because they alter the composition of the microflora. This changes the metabolic activity of the colon, which could well result in altered lipid and cholesterol metabolism. We have studied the cholesterol lowering properties of viscous fibre and we think that combining them with fructans will result in an additional benefit.

Furthermore, we are very interested to look at the effects of fructans combined with soy proteins and isoflavenoids. Isoflavenoids may be antioxidants and soy is a rich source of isoflavones. The isoflavones found in soy may have benefits on lipid metabolism both by their antioxidant action and by other metabolic pathways. Soy isoflavones become active after transformation by the colonic microflora and this is where fructans come in. The selective colonic fermentation of fructans increases bifidobacterial populations, which may enhance the production of isoflavones, especially equol, from soy. The combination of inulin and soy isoflavones could thus have a synergistic effect on the reduction of blood lipids and the prevention of cholesterol oxidation. This dietary approach could be very important in the fight against cardiovascular disease.

Fibres in general, and fructans in particular, combined with plant proteins, plant sterols and nuts, especially almonds, in the diet could form a powerful strategy or dietary portfolio for risk management of heart disease, and possibly the prevention of other diseases too. So, I really think that the combination of fibres and fibre-like substances with other active ingredients in the diet will become a very important tool to maximise nutritional effectiveness.

Although I have made the distinction between viscous and non-viscous fibre in relation to the rate of nutrient digestion, it has recently become clear that many other aspects of carbohydrate foods, such as the food form or the presence of antinutrients, may exert an influence. This has led to a classification, especially of starchy foods, in terms of the degree to which consumption of equicarbohydrate portions of different foods subsequently raise the blood glucose levels, the so-called glycemic index of a food. Use of such data may maximise the effectiveness of high-carbohydrate and high-fibre diets in the management of diabetes and related disorders.

The beneficial potential of inulin and oligofructose in Western lifestyle diseases

Inulin-type fructans are non-digestible oligo- and polysaccharides for which a wide range of scientific observations in animals and humans are available that demonstrate an array of potential health benefits. Among these health effects there is a reduced risk of developing so-called Western lifestyle diseases, including atherosclerotic cardiovascular disease associated with dyslipidemia and insulin resistance, obesity and type-2 diabetes (Roberfroid, 2002).

Hyperlipidemia and cardiovascular disease

Coronary heart disease (CHD) is one of the major causes of death and disability in industrialised countries and the prevalence of CHD is strongly correlated to lifestyle factors, including diet. Diets that are high in mono-unsaturated fatty acids, dietary fibre and low glycemic index foods appear to be advantageous in protection against insulin resistance, control of blood glycemia and blood lipids (Hung et al., 2003; Jenkins et al., 2003a). It is estimated that a 10% reduction in cholesterol levels in adults would result in a 10-25% reduction in the CHD mortality rate. There is now much evidence that elevated plasma triacylglycerol (TAG) levels are an independent lipid risk factor for CHD (Williams, 1997). The key features of the lipid profile with a

high risk for CHD are moderately raised TAG, elevated concentrations of TAG-rich remnant particles (chylomicron or VLDL remnants), low HDL-cholesterol and raised, small dense LDL-cholesterol. Individuals with this collection of lipid abnormalities, termed the atherogenic lipoprotein phenotype, have a 3- to 6-fold greater risk of CHD (Williams et al., 2002).

There is much evidence that insulin resistance is the primary metabolic component which leads to excessive synthesis and secretion of VLDL, impaired removal of chylomicron and VLDL particles and elevated blood TAG levels. Evidence that impaired TAG tolerance and elevated TAG levels are the key lipid abnormality of a dyslipidemia linked with a markedly higher risk of CHD, has generated a great deal of interest in possible dietary strategies that can reduce circulating TAG levels and which might have beneficial effects on insulin resistance.

Current dietary strategies implicate adherence to a low-fat/low-saturated fat diet (Taylor et al., 1998). However, such diets are difficult to maintain on a longterm basis and their efficacy diminishes over time (Pereira et al., 2002). Moreover, high-carbohydrate/low-fat diets that contain mainly simple carbohydrates, can have the undesirable side effect to increase plasma TAG concentrations (Letexier et al., 2003).

The addition of non-digestible oligosaccharides, which have a beneficial effect on lipid metabolism, could be one approach to reduce total cholesterol and TAG concentrations, and to avoid the risk of elevated TAG concentrations during consumption of a high-carbohydrate diet.

Animal studies

In animals, the addition of chicory fructans in the diet is able to counteract triglyceride accumulation in the liver and/or in the serum, depending on the type of diet and the pathophysiological status of rats (Delzenne et al., 2002a).

Fiordaliso et al. (1995) observed a decrease in plasma triglycerides, phospholipids and total cholesterol in rats fed a standard diet containing 10% oligofructose (OFS, Raftilose® P95). The triglyceride-lowering effect was observed after one week and lasted for at least 16 weeks. It was associated with a reduction in plasma VLDL, due to a reduction in the number rather than a change in the composition of the VLDL particles, while both LDL and HDL remained unchanged.

In lean rats, OFS feeding (10%) significantly decreased TAG and phospholipid (PL) concentrations in blood and liver. It did not affect the blood non-esterified fatty acid concentrations but reduced the capacity of isolated hepatocytes to synthesise and secrete TAGs from labelled acetate. The activity of fatty acid synthase (FAS), a key lipogenic enzyme, was also significantly decreased, as well as postprandial glycemia and insulinemia (Kok et al.,1996a; Delzenne et al., 2001).

Supplementation with OFS also protected rats against lipid accumulation in the liver and hyperinsulinemia induced by fructose, although it could not prevent the hypertriglyceridemia (Kok et al.,1996b; Busseroles et al., 2003).

The addition of chicory OFS or inulin to a high-fat diet reduced post-prandial triglyceridemia, protected rats against the increase in free cholesterol serum level and almost completely inhibited FAS activity. It did not prevent the high-fat-induced hepatic accumulation of TAG, PL and cholesterol, suggesting that fructans supplementation in this type of diet affects only circulating triglycerides, PL and cholesterol. Histochemical analysis also showed smaller lipid droplets in the liver of OFS-supplemented rats as compared to control high-fat rats (Kok et al.,1998a; Delzenne et al., 1999a; Delzenne et al., 2002a).

These findings were confirmed by Trautwein et al. (1998) in hamsters. The addition of chicory inulin to the diet exerted a significant hypocholesterolemic and TAG effect, especially at dietary levels of 12 and 16%. Dietary inulin specifically decreased VLDL cholesterol, whereas LDL and HDL cholesterol were not significantly affected. Daily fecal bile acid excretion tended to be greater in inulin-fed hamsters, daily neutral sterol excretion was not affected, suggesting that cholesterol digestibility was not impaired. Interestingly, fecal cholesterol concentrations tended to be higher in inulin-fed hamsters, whereas the concentration of coprostanol was lower. This suggests a reduced bacterial cholesterol degradation as a result of inulin ingestion.

Using an animal model of familial hypercholesterolemia and atherosclerosis, Mortensen et al. (2002) showed that addition of 10% long-chain chicory inulin (Raftiline®HP) to the diet reduced total plasma cholesterol (lower concentrations in LDL, IDL and VLDL, but not in HDL) and increased HDL:LDL-ratio. Triglyceride concentration in plasma and lipoproteins were not significantly affected by long-chain inulin. Aortic atherosclerosis expressed as the ratio intima/media was 15% lower with inulin compared to controls, but this difference was not statistically significant.

These data suggest that a decreased de novo lipogenesis in the liver through modulation of FAS-activity, combined with a decrease in fatty acid esterification, causes a reduction in VLDL-TAG secretion in fructan-fed rats. The lower insulin

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level in the serum of OFS-fed rats could explain, at least partly, the metabolic effect induced by such non-digestible carbohydrates since the transcription level of FAS is primarily activated by glucose and insulin.

In high-fat diets, inulin and OFS decrease serum TAG through an extra-hepatic event by enhancing TAG-rich lipoprotein catabolism (increased activity of lipoprotein lipase in rat adipose tissue). Lipoprotein lipase is the capillary-bound enzyme responsible for the clearance of dietary and endogenous (VLDL) triglycerides.

On the other hand, fructan addition in the diet of rats has been shown to increase the postprandial serum glucose-dependent insulinotropic polypeptide (GIP) level and to increase glucagon-like peptide-1 (GLP-1) concentration in the caecal tissue and in the portal serum. GIP has been shown to stimulate or inhibit lipolysis in adipocytes and to stimulate lipoprotein lipase in cultured peradipocytes. GLP-1 exerts insulinomimetic effects in liver, muscle and fat. However, the exact contribution of these two hormones in the antilipogenic effect of fructans remains to be clarified (Kok et al., 1998b; Delzenne et al.,1998; Delzenne et al., 2000; Delzenne et al., 2002b). Moreover, fructans could suppress serum cholesterol through an enhanced secretion of fecal neutral steroid and bile acids (Delzenne et al., 2001; Pereira et al., 2002). Other mediators, for instance propionate, could also be involved. OFS and inulin are largely fermented in the ceco-colon, leading to the production of short-chain carboxylic acids and consequently the portal concentrations of acetate and propionate are increased (Roberfroid, 2000).

Human studies

In humans, attempts to reproduce the lipid-lowering effects from animal studies have generated less consistent results (Jenkins et al., 2000a).

Viscous soluble fibres affect total and LDL-cholesterol fractions, largely through inhibition of bile acid absorption and metabolism, whereas fructans appear to lower the triglyceride-rich fractions through secondary effects after fermentation in the large bowel (Delzenne et al., 1999b).

In young normolipidemic women, the daily intake of 14 g inulin had no lipid-lowering effect although there was a significant reduction of the LDL:HDL cholesterol ratio (Pedersen et al., 1997).

Although young healthy men, consuming 20 or 15 g of OFS during 4 and 3 weeks, respectively, did not have changes in their blood lipid concentrations (Luo et al., 1996; Van Dokkum et al., 1999), a significant decrease in plasma total cholesterol and TAG levels was reported in men who consumed 50 g of a rice-based ready-to-eat cereal containing 9 and 18% inulin during four weeks (Canzi et al., 1995; Brighenti et al., 1999).

The TAG levels remained even significantly lower one month after cessation of inulin supplementation. No effect on HDL cholesterol was observed, but breath hydrogen was significantly elevated during the inulin diet. Serum cholesterol levels were positively correlated to the daily excretion of secondary bile acids.

Davidson et al. (1998 & 1999) showed that the supplementation of 18 g inulin (Raftiline®ST) per day during 6 weeks could blunt the hypercholesterolemic effects of high-fat foods in men and women with baseline significantly elevated LDL-cholesterol. During inulin treatment, small declines were observed for both LDL-and total cholesterol.

Although serum triglycerides and the LDL:HDL-ratio were not significantly altered, a non-significant trend towards favorable changes was observed.

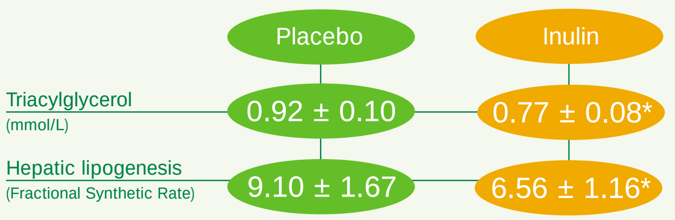
The addition of chicory inulin (Raftiline®HP) to a moderately high-carbohydrate/low-fat diet has been demonstrated to have a beneficial effect on plasma lipids in healthy subjects by significantly decreasing hepatic lipogenesis and plasma TAG concentrations. There was no significant effect on cholesterol synthesis, plasma cholesterol concentrations and adipose tissue messenger RNA concentrations (Letexier et al., 2003).

In healthy but slightly hyperlipidemic adults, the consumption of 10 g/day inulin (Raftiline®HP) significantly reduced fasting triglycerides (-19% after 8 weeks) and insulin levels (-17% after 4 weeks and -10% after 8 weeks), whereas no effects on cholesterol could be observed (Williams et al., 1998; Jackson et al., 1999).

The authors showed that the daily addition of inulin resulted in lower plasma TAG levels, particularly in subjects whose fasting TAG levels were greater than 1.5 mmol/L. No effect on fasting glucose concentrations and other lipid variables were seen.

In hypercholesterolemic men the daily intake of 20 g chicory inulin during three weeks reduced serum triglycerides by 40 mg/dL and tended to lower serum cholesterol. This improvement in lipid parameters was accompanied by a change in the short-chain fatty acids (SCFA) profile. The decrease was dependent on the concentration of serum cholesterol: subjects with serum cholesterol levels above 250 mg/dL tended to have the greatest reduction after inulin supplementation. Insulin and glucagon levels were

Consumption of Raftiline®HP affects lipid metabolism After Letexier et al. (2003)



Consumption of Raftiline®HP (10 g/day) during 6 weeks by healthy volunteers (n=8) significantly ($p < 0.05$) decreased triacylglycerol levels in the blood as well as hepatic lipogenesis.

increased 1 hour after glucose load, maybe because of the increase in SCFA (Causey et al., 2000).

Recent data relative to the protective effect of dietary fructans on hepatic steatosis in animals have been confirmed in a pilot study in humans.

Non-alcoholic steatohepatitis (NASH) constitutes one of the most frequent liver disorders, occuring together with syndrome X, in overweight and obese people (Delzenne et al., 2000; Daubioul et al., 2003).

The different outcomes in animal versus human studies may be explained by differences between species, their physio-pathological state and the relative doses used. In animals, the inhibition of hepatic FAS has been identified as the major mechanism in the TAG lowering effects of inulin and oligofructose. However, this pathway is relatively inactive in man unless a high-carbohydrate diet is fed. The variability in response to fructan supplementation also may be a reflection of differences in the background diet, the experimental foods used and the serum lipid composition at the start of the treatment (Delzenne, 1999; Roberfroid, 2000; Parks, 2002; Pereira et al., 2002; Jackson et al., 1999; Williams et al., 2002).

More studies should be performed in patients with a higher lipogenic activity, a metabolic characteristic prone to occur in people with a high BMI, eating high-calorie/high-carbohydrate diets. Especially in subjects with type-2 diabetes or those with a dyslipidemia characteristic of insulin resistance (where triglyceride rather than cholesterol is the primary lipid abnormality seen) further research would be of particular value (Delzenne et al., 2001a; Williams et al., 2002). The data support the notion that fructans attenuate lipid parameters to a more physiological level in subjects with elevated parameters.

Diabetes

Diabetes is a plurimetabolic disease, characterised mainly by abnormalities in the glucose metabolism which leads to the development of acute and long-term complications. It is expected that between 1995 and 2025 the number of people with type-2 diabetes will increase with 27% from 6 to 7.6% in developed countries and with 48% from 3.3 to 4.9% in developing countries.

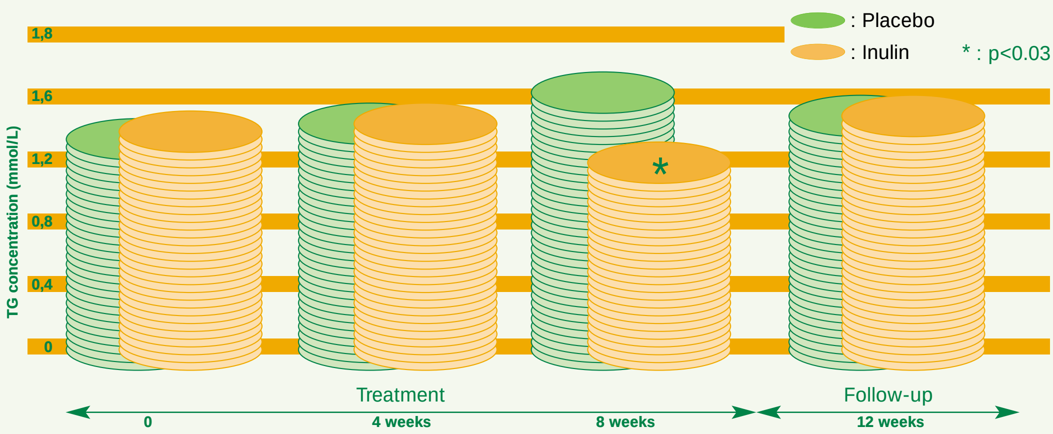
Convincing evidence shows that in diabetic patients diets high in dietary fibre and carbohydrates with a low glycemic index decrease postprandial plasma glucose, insulin and triglyceride concentrations and have a hypocholesterolemic effect (Jenkins et al., 1995, 1996 & 2000b; Del Toma et al., 1988; Hung et al., 2003). The beneficial metabolic effects of dietary fibre are long-lasting and clinically relevant, as is shown by the decrease in plasma glycosylated haemoglobin levels, the reduction of hypoglycemic episodes and the improvement of the cardiovascular profile, both in type-1 and type-2 diabetic patients (Giacco et al., 2002; Hu et al., 2001; Rizkalla et al., 2002).

The metabolic improvements from dietary fibre consumption include a delay of glucose absorption, an increase in hepatic extraction of insulin, increased insulin sensitivity at the cellular level and binding of bile acids (Tabatai & Li, 2000; Jenkins et al., 2002b).

Agheli et al. (1996) have shown in a rat model of diet-induced insulin resistance that supplementation with fructans prevented some lipid disorders, lowered fatty acid synthase activity in the liver and tended to raise this activity in the adipose tissue. Feeding diabetic rats a diet containing 10% oligofructose for 2 months decreased postprandial glycemia despite a lack of modification of the glycemic or insulinemic response to a saccharose or maltose load (Delzenne et al., 2001a).

In diabetic patients the results obtained so far are not conclusive. Consumption of 8 g/day fructans for two weeks decreased total cholesterol and LDL-cholesterol in type-2 diabetic patients by 8 and 10%, respectively. This treatment also significantly reduced blood glucose levels, especially in hypercholesterolemic subjects. Circulating TAG did not change (Yamashita et al., 1984). In another study, consumption of 15 or 20 g/day fructans for 4 weeks had no effect on glucose and lipid metabolism.

Reduction of blood triglycerides After Jackson et al. (1999)



Fasting plasma triglycerides in subjects (n=27/group) receiving either inulin (10 g/day Raftiline®HP) or placebo (10 g/day maltodextrin) for 8 weeks with follow-up measurement at 12 weeks.

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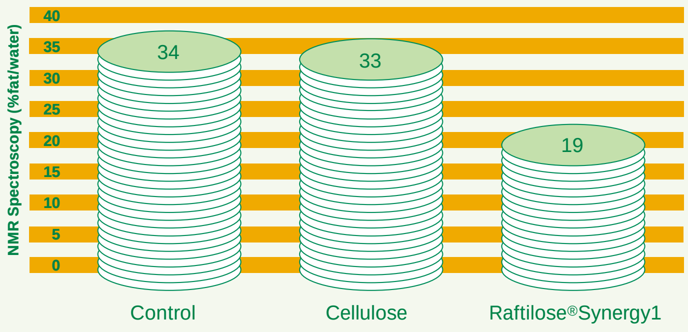
Fasting plasma glucose and insulin concentrations or basal hepatic glucose production were not modified. The plasma glucose response to a fixed exogenous insulin bolus and erythrocyte insulin binding did not differ, and serum TAG, total and HDL-cholesterol, free fatty acids, apolipoproteins A1 and B and lipoprotein (a) concentrations were not modified (Luo et al., 2000; Alles et al., 1999).

Obesity

The prevalence of obesity has increased dramatically in recent years in all age groups both in developed and in developing countries. It is considered as one of the fastest growing epidemics, now affecting 10-40% of the adult population in Western countries. Obesity is a major risk factor for the development of chronic diseases such as type-2 diabetes, cardiovascular disease, certain cancers, and it is associated with a reduction of life expectancy. The risk of diabetes is particularly increased by obesity: 80-95% of the increase in diabetes can be attributed to obesity and overweight with abdominal fat distribution (Astrup, 2001).

There is robust evidence to support that an energy-dense, high-fat diet and physical inactivity are independent risk factors for obesity, whereas diets low in fat, high in protein and complex carbohydrates with a low glycemic index contribute to the prevention of weight gain in normal weight subjects and to weight loss in overweight subjects (Astrup, 2001; Rizkalla et al., 2002).

Effect of Raftilose®Synergy1 on liver fat accumulation After Daubioul et al. (2002)



Liver fat abundance measured by nuclear magnetic resonance (NMR) spectroscopy in Zucker rats fed a control diet or that diet enriched with cellulose or Raftilose®Synergy1. The results are expressed as weighted proton density of fat relative to water. (* $p<0.05$)

Daubioul et al. (2000 & 2002) clearly showed that chicory inulin and oligofructose added to the diet of obese Zucker rats decrease body weight gain, visceral and epididymal fat mass and triglyceride accumulation in the liver and thus have beneficial effects on liver steatosis. These results support the fact that a decrease in the weight of visceral fat mass, and/or the subsequent decrease in non-esterified fatty acid availability, might constitute an important metabolic event in the regulation of hepatic fatty acid metabolism, at least in obese animals (Delzenne et al., 2002b).

Furthermore, oligofructose fed to obese Zucker rats induced a satietogenic effect leading to a decrease in food intake during the first 3 weeks of treatment (Daubioul et al., 2000). Food intake is regulated by small peptides that are released in the gastro-intestinal tract, such as GLP-1 and ghrelin. It was discovered recently that the secretion and regulation of these peptides is severely disturbed in people with weight abnormalities such as anorexia nervosa, obesity and type-2 diabetes compared to normal-weight patients (Tschöp et al., 2001; Shiiya et al., 2002). Addition of 10% chicory inulin or oligofructose to the diet of rats for 3 weeks significantly decreased the dietary energy intake, leading to a reduction in epidydimal fat mass. The level of GLP-1, which has an anorexigenic action, was significantly increased. When rats were during their fasting state, the plasma active ghrelin level, known to stimulate food intake, was significantly reduced in rats consuming the fructan diet compared to the control rats (Cani et al., Submitted).

As a result, chicory inulin or oligofructose in the diet of rats positively modulated the intestinal peptides involved in the metabolic regulation of weight gain.

One of the metabolic abnormalities designated as part of syndrome X is NASH, a frequent pathology occurring mainly in overweight and obese people and in patients with diabetes or hyperlipidemia. It is diagnosed in 85% of severely obese people (Delzenne et al., 2002b). The disruption of insulin regulation, another feature associated with syndrome X, has been implicated as a factor in the pathogenesis of NASH, as well as disturbed fatty acid metabolism leading to fat accumulation in the liver. In a recent pilot study in patients diagnosed with NASH by means of a liver biopsy, the dietary supplementation with 16 g/day OFS (Raftilose®P95) during 8 weeks had a slightly positive effect on serum aminotransferase. Although this effect could indicate an improvement of liver function, the liver ultrasonography did not show any difference in liver size. Contrary to the animal model, OFS supplementation had no effect on food habits, BMI or fat mass in this study. Serum glucose and insulin levels did not change, but glucagon levels were significantly higher in OFS-fed patients. Glucagon could orientate hepatic fatty acid metabolism towards oxidation rather than esterification. The findings in this pilot study interestingly support the improvement of hepatic enzyme activity in NASH patients receiving an oligofructose supplementation (Daubioul et al., 2003).

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FREQUENTLY ASKED QUESTIONS

How much inulin does our daily diet contain? How much extra inulin do we need?

Inulin is naturally present in many vegetables, fruits and cereals that are part of our daily diet. Leek, onions, banana, wheat and garlic are the main sources that contribute to the inulin intake in most parts of the Western world. The intake varies somewhat between 1-4 g per day for an American adult and 3-11 g per day for his European counterpart. Occasionally, people could have peak intakes when certain inulin-rich dishes are consumed, such as an onion or leek soup or a salsify dish. Furthermore, the intake varies with age, gender, race, season, but also region, as cultural differences heavily determine eating pattern and food preference.

Dietary fibre is known to alleviate daily digestive discomforts such as constipation and stool irregularity, but also to prevent the development of lifestyle diseases in the long term, such as obesity, type-2 diabetes or cardiovascular disease. Current recommendations for dietary fibre intake are set at 30 g/day. Most people however, are far from reaching this amount. Inulin and oligofructose could add up to the daily fibre requirements in a very convenient way.

Furthermore, inulin and oligofructose have been shown to induce beneficial physiological effects beyond those of classical fibres, such as a selective stimulation of our good intestinal bacteria (bifidobacteria) or an improvement of calcium and magnesium absorption. Such benefits are seen with daily inulin or oligofructose doses of 5-8 g on top of our normal diet. This is difficult to achieve through the intake of fruits and vegetables (you need 5 onion bulbs to get 1 g of inulin) but easily obtained by consuming food products enriched with inulin and oligofructose, such as e.g. dairy products, breakfast cereals and baked goods.

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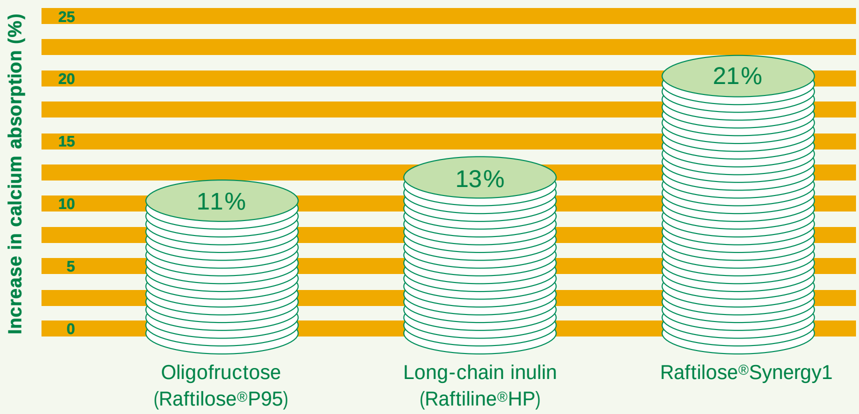
MONITOR

Enhanced effect of Raftilose®Synergy1 on intestinal calcium absorption

This study compared the effect of inulin-type fructans with different chain length and chain branching on mineral absorption. Adult male rats were fed for 28 days either a fibre-free basal purified diet or a diet enriched with 10% oligofructose (Raftilose®P95), with 10% long-chain inulin (Raftiline®HP), with a specific combination of long-chain inulin and oligofructose (Raftilose®Synergy1), or with a branched-chain inulin.



All the fructans tested led to a considerable cecal fermentation and significantly increased the intestinal absorption and retention of magnesium. Apparent calcium absorption increased at least 11% for all fructans with a significant increase in absorption (26%) and retention (25%) by supplementation with Raftilose®Synergy1. So, the specific chain length distribution of the fructans present in Raftilose®Synergy1 was shown to have an increased effect on mineral absorption in comparison with its separate constituents or branched-chain inulin. It is hypothetised that oligofructose, a short-chain fructan, serves as a starter fuel for selective bifidogenic growth and metabolic acitivity in the proximal colon, which is then maintained in distal parts of the colon by the more slowly fermented long-chain inulin. The presence of both short-chain, rapidly fermentable, and long-chain, more slowly fermented, fructans could thus allow maintenance of a high fermentation activity and therefore improved mineral absorption throughout the large intestine.

Coudray C., Tressol J.-C., Gueux E. & Rayssiguier Y. (2003). Effects of inulin-type fructans of different chain lenghts and type of branching on intestinal absorption and balance of calcium and magnesium in rats. Eur J Nutr, 42, 91-98.

Inulin and oligofructose modulate immune function

Although a number of studies have shown that the addition of oligofructose and inulin to the diet increases resistance to systemic challenges with pathogens, their effects on specific systemic immune cell populations had not yet been defined.

In this study, selected systemic immune variables were measured in B6C3F1 mice fed diets containing either 10% cellulose, 10% inulin (Raftiline®HP), 10% oligofructose (Raftilose®P95), or 2,5% oligofructose and 7,5% cellulose.

Total white blood cell counts were within the normal range for all groups. White blood cell counts for mice fed the fructan-containing diets were similar to each other, but were significantly lower than those for mice fed the control diet. Differential counts revealed that the ratios of white blood cell types did not differ among the groups. The depressed WBC count for all treatments suggests a shift away from the hematopoeitic cytokines IL-3, IL-5 and GM-CSF which are associated with a Th2 state.

Natural Killer Cell activity and macrophage phagocytosis were enhanced in mice fed the oligofructose (OFS) and inulin diets, but not in the OFS-cellulose group, indicating a dose-response relationship. These findings suggest that dietary fructans trigger a shift to a greater dependence on Th1 cell-mediated immunity. Apparently oligofructose and inulin do not elicit an increase or redistribution of the lymphocyte populations (CD4/CD8 and T/B). Also the only enteric immune function measured, fecal IgA, did not differ among the four groups, further supporting the premise that dietary fructans induce a shift to Th1 (non-IgA producing) immunity.

Kelly-Quagliana K.A., Nelson P.D. & Buddington R.K. (2003). Dietary oligofructose and inulin modulate immune functions in mice. Nutr Res, 23, 257-267.

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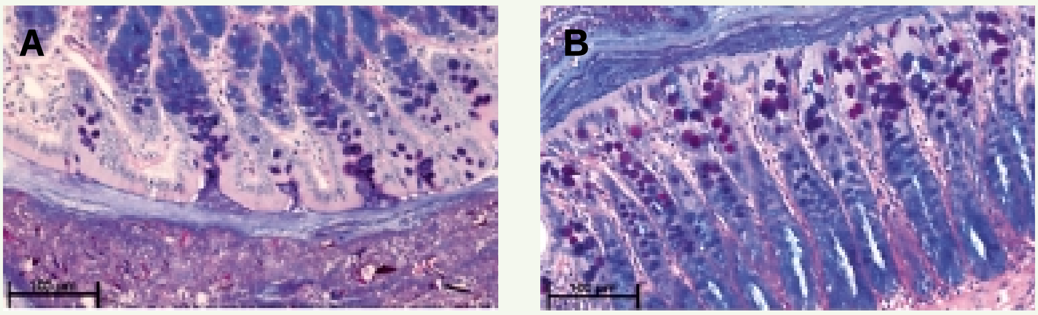
Fructans stabilise the gut mucosal barrier

The effects of dietary oligofructose (Raftilose®P95) and inulin (Raftiline®HP) in the diet on mucosal morphometry, thickness of the epithelial mucus layer and histochemical composition of intestinal mucosubstances in the distal jejenum and colon were investigated by comparing germfree (GF) rats, rats harbouring a diassociated (DA) flora of Bacteroides vulgatus and Bifidobacterium longum and rats associated with a human fecal flora (HFA). They were fed either a standard diet (CT) or CT with 5 g/100 g oligofructose (OFS) or inulin.

OFS and inulin supplementation resulted in higher villi and deeper crypts in DA-, but not in GF-rats, which suggests that fructans do not affect the epithelial morphometry in the jejenum directly but that it is an indirect effect of their fermentation by intestinal bacteria. DA- and HFA-rats had a thicker colonic epithelial mucus layer and a higher number of goblet cells than GF-rats, features that were all enhanced by OFS and inulin supplementation. Both in the CT and fructan-supplemented group, bacterial colonisation of GF-rats increased neutral mucins in the distal jejenum and colon. DA-rats had more acidic mucins in the colon than GF-rats, predominantly sulfomucins in the OFS and inulin groups, while sialomucins dominated in the CT group. Differences in the amounts of sulfomucins and sialomucins present could have important effects on the susceptibility of epithelial mucins for degradation by bacterial enzymes. The number of mucosa-associated bifidobacteria in the colon of DA- and HFA-rats was higher in the OFS and inulin groups. Fructans increased the number of bifidobacteria in the lumen only in DA-rats. This study showed for the first time that inulin-type fructans in the diet can change the mucosal architecture, released mucins and mucosa-associated bacteria in DA and HFA-rats. It is probable that such dietary manipulation could be of benefit for both the protection of an intact intestinal epithelium and the therapy of a disturbed mucosal barrier.

Kleessen B., Hartmann L. & Blaut M. (2003). Fructans in the diet cause alterations of intestinal mucosal architecture, released mucins and mucosa-associated bifidobacteria in gnotobiotic rats. Br J Nutr, 89, 597-606.



Histological analysis of the colonic tissue of human flora-associated rats fed a standard diet (A) or a standard diet supplemented with chicory inulin (B). A combination of Alcian Blue, pH 2.5 and periodic acid-Schiff staining was used to distinguish acidic (dark blue) and natural (red) mucins.

A purple colour indicates the presence of poch acidic and neutral mucins. The epithelial mucus layer was thicker in fructan-fed rats.

Benefits of oligofructose and inulin in animal diets

This article provides an extensive review of the effects of inulin and oligofructose on gastrointestinal characteristics (microflora, pathogen control, epithelial cell proliferation, putrefactive compound production, fecal characteristics, and nutrient digestibility) and systemic metabolism of carbohydrates, nitrogen, lipids, and minerals in dogs, cats, horses, calves, pigs, poultry, and rabbits. Oligofructose appears to reduce small intestinal bacterial overgrowth in dogs, improves colonic bacterial balance in cats, and has a mixed effect on the colonic microflora of dogs. Small intestinal absorptive capacity and colonic epithelial cell proliferation are improved by oligofructose supplementation in dogs. Oligofructose also tends to decrease fecal putrefactive compounds. Both oligofructose and inulin have a modest effect on fecal characteristics and nutrient digestibility when compared with traditional fibre sources. Carbohydrate, nitrogen and lipid metabolism are positively affected, but specific effects vary between inulin and oligofructose.

Moreover, intake of inulin and oligofructose and considerations in their supplementation to animal diets are discussed. Growth performance and meat production in livestock in response to inulin and oligofructose supplementation are addressed. Colonic concentrations of beneficial bacteria are increased by oligofructose in pigs and quails. Oligofructose supplementation reduces pathogen colonisation and contamination in poultry. It increases cecal and colonic epithelial cell proliferation in young pigs. Both inulin and oligofructose reduce ammonia in pigs and rabbits.

Oligofructose has a modest effect on fecal characteristics of swine. It increases ileal digestibility of nutrients in pigs and total tract digestibility of zinc in swine without significantly impacting on the absorption or retention of other minerals. Inulin and oligofructose affect weight gain and feed efficiency in pigs and early-weaned calves. Oligofructose also improves growth performance and meat production of broiler. Data from poultry suggest that oligofructose may be as effective as antibiotics in the control of pathogens and enhancement of growth performance. Finally, directions for future research are presented.

Flickinger E.A., Van Loo J. & Fahey G.C. (2003). Nutritional responses to the presence of inulin and oligofructose in the diets of domesticated animals: a review. Critical Reviews in Food Science and Nutrition, 43, 3-43.

Inulin and oligofructose potentiate cancer radiotherapy

Inulin (Raftiline®HP) and oligofructose (Raftilose®P95) were incorporated in the diet (15%) of mice that were injected with transplantable liver tumour (TLT) cells. Dietary supplementation with fructans inhibited tumour growth even without additional anticancer treatment.

When the approximate liver tumour reached a volume of 1000 mm^3, the mice were locally treated with irradiation therapy. There was a distinct tumour growth inhibitory effect of both inulin and oligofructose compared with the mice on a basal diet when treated with radiotherapy (10 Gy), without increased toxicity. It is unclear by which mechanism fructans potentiate the tumour growth inhibition. Fructan fermentation in the gut induces changes in bacterial composition and could change glucose availability, the production of insulin-like growth factor and endogenous fatty acid synthesis, all of which are implicated in the metabolism, and thus indispensable for the growth, of tumour cells.

Taper H.S. & Roberfroid M.B. (2002) Non-toxic potentiation of cancer radiotherapy by dietary oligofructose or inulin. Anticancer Res. 22, 3319-3324.

Fermentable dietary fibres enhance magnesium absorption

The effect of dietary fibre on mineral absorption depends largely on its nature and characteristics and also on mineral homeostasis.

This article reviews a number of animal and human studies about the effects of dietary fibres on magnesium (Mg) absorption. Studies conducted on different types of fermentable carbohydrates have confirmed their beneficial effect on Mg absorption in different animal species.

To date, four human studies confirm the increase of Mg absorption by some fermentable oligo- and polysaccharides. It is concluded that Mg absorption as well as Mg status can be improved by encouraging a greater consumption of specific dietary fibre-rich products, in particular those which are highly fermentable.

Coudray C., Demigné C. & Rayssiguier Y. (2003). Effects of dietary fibers on magnesium absorption in animals and humans. J Nutr, 133, 1-4.

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Oligofructose protects against oxidative stress

A high fructose diet has hypertriglyceridemic and pro-oxidative effects in rats compared with a starch-based diet. In this study, modification of the impact of fructose on oxidative stress parameters by supplementation with oligofructose (OFS) was assessed. Rats were fed either a high fructose or a starch-based diet, both with or without the addition of 10% oligofructose (Raftilose®P95) for 4 weeks.

Regardless of the diet, OFS elicited an enlargement of the caecum and led to a significant rise in the caecal short-chain fatty acids (SCFA) pool. Fructose feeding was associated with a rise in insulin plasma concentrations (+63%) in the control groups, whereas no significant difference was observed in the OFS-fed rats. This suggests that OFS may affect the availability of fructose. Plasma leptin concentration was reduced (50%) in the OFS-supplemented fructose group compared with the three other groups. This result is consistent with a possible improvement of the fructose-induced insulin resistance and/or hyperinsulinemia.
Fructose feeding also increased plasma and liver triglyceride (TG) levels, while OFS-supplementation prevented hyperlipemia and TG accumulation in the liver. This effect appears to be due mostly to reduced secretion of VLDL particles from the liver and appears to be associated with reduced gene expression and lipogenic enzyme activity. OFS consumption also tends to prevent the decreased plasma vitamin E:TG ratio in rats fed the fructose diet. High plasma thiobarbituric acid-reactive substances (TBARS) values were found in fructose-fed rats when compared to the starch-fed rats. Supplementation of the diet with OFS protected against the pro-oxidative effect of fructose, which was demonstrated by unchanged plasma TBARS, reduction of urinary TBARS values, reduction of heart tissue susceptibility to peroxidation in fructose-fed rats. An increased fructose consumption combined with the low intake of dietary antioxidants in industrialised countries, may affect the development of the cluster of metabolic abnormalities designated as syndrome X, which includes obesity, type-2 diabetes and cardiovascular disease. This study supports the potential benefits of OFS with regard to syndrome X, given its positive effect against fructose-induced hyperlipemia, insulin resistance and oxidative stress.

Busserolles J., Gueux E., Rock E., Démigné C., Mazur A. & Rayssiguier Y. (2003). Oligofructose provides protection against the hypertriglyceridemic and pro-oxidative effects of a high fructose diet in rats. J Nutr, 133(6):1903-1908.

Inulin and oligofructose improve quality of broiler chickens

The objective of this research was to study the effectiveness of adding inulin (Raftifeed®IPF) or oligofructose (Raftifeed®OPS) to the diet on improvement of growth performance, serum cholesterol levels and intestinal characteristics in broilers. After six weeks of consumption, the addition of 1% oligofructose or inulin had no significant effect on body weight, ready-to-cook (RTC) carcass weight, feed:gain ratio and gut length of male birds. However, the carcass percentages of the inulin males were higher than those of the controls, indicating a higher RTC-dressing yield. In female birds, adding 1% oligofructose increased body weights (in average more than 10%), carcass weights, carcass percentages and gut lengths. The feed:gain ratio also improved. The fructan-fed birds had a more developed small intestine and the female birds had a more dense ileal villi distribution. Both inulin and OFS reduced serum cholesterol and abdominal fat in male and female broilers.

Yusrizal & Chen Y.C. (2003). Effect of adding chicory fructans in feed on broiler growth performance, serum cholesterol and intestinal length. Int J Poultry Sci, 2, 214-219.

Effects of inulin and oligofructose on fecal and intestinal microflora of chickens

The effectiveness of adding 1% inulin (Raftifeed®IPF) or oligofructose (Raftifeed®OPS) to the diet of chickens to reduce the presence of pathogenic micro-organisms and the emission of ammonia was evaluated. Oligofructose in the diet reduced volatile ammonia and fecal

pH in fresh feces during the first four weeks of cultivation. No significant reduction was observed during weeks 5 and 6, which might be due to the change in the diet at week 5 (from a starter to a grower diet). Little or no effects were observed for inulin. No differences in moisture contents among the fecal samples were observed, although inulin- and oligofructose-treated broilers had lower fecal moisture contents during weeks 4 and 5.

Total aerobe and E. coli counts were significantly reduced in the oligofructose-treated male birds at week 4. Campylobacter levels decreased both with inulin and oligofructose supplementation in males. In female birds the effects were less consistent: Lactobacilli counts were increased in the gizzard and small intestine by oligofructose and in the large intestine by both inulin and oligofructose.

Furthermore, addition of oligofructose and inulin significantly reduced Campylobacter counts in the large intestine and Salmonella counts in the cecal content.

Yusrizal & Chen Y.C. (2003). Effect of adding chicory fructans in feed on fecal and intestinal microflora and excreta volatile ammonia. Int J Poultry Sci, 2, 188-194.

Effect on calcium bioavailability depends on fructan chain length

Oligofructose (Raftilose®P95), inulin (Raftiline®HP) and a mixture of 92% inulin and 8% oligofructose have been compared in terms of their impact on calcium absorption, bone density and excretion of collagen cross-links in young adult male rats. In the inulin-fed group, bone mineral density was significantly higher in the femurs, and bone mineral content was significantly higher in the spine. The urinary excretion of fragments of Type 1 collagen, a marker of bone resorption, was decreased in all groups over the 4 weeks of feeding, but the decrease was most significant in the inulin-fed group. Feeding inulin significantly increased bone mineral content and bone density.

Kruger M.C., Brown K.E., Collett G., Layton L. & Schollum L.M. (2003). The effect of fructooligosaccharides with various degrees of polymerization on calcium bioavailability in the growing rat. Exp Biol Med, 228, 683-688.

Prebiotics and calcium bioavailability

This review critically assesses the available data on the effects of prebiotics on calcium bioavailability in the context of human physiology and explains the underlying cellular and molecular mechanisms. It is concluded that inulin, oligofructose, galacto-oligosaccharides and lactulose stimulate calcium absorption and retention in rats. In some animal studies the enhanced calcium absorption leads to an improved bone status. There is relatively good evidence of a beneficial effect of prebiotics on calcium bioavailability in rats. In humans, a few studies have shown a stimulatory effect of fructans on true intestinal calcium absorption, at least in subgroups of the population which have increased calcium requirements (adolescents, postmenopausal women).

The review also highlights future research areas that may help in the evaluation of prebiotics as potential ingredients for functional foods aiming at the enhancement of calcium bioavailability and the protection against osteoporosis.

Cashman K. (2003). Prebiotics and calcium bioavailability. Curr Iss Intest Microbiol, 4, 21-32.

Health and nutritional benefits of inulin and oligofructose

This article reviews the health benefits as well as the biochemical basis of the physiological effects of inulin and oligofructose: their prebiotic and bifidogenic properties, the beneficial effects of their fermentation products in the gastrointestinal tract, their effect on constipation, on mineral absorption, on glycemia/insulinemia, on lipid metabolism and cholesterolemia, on uremia and nitrogen/urea disposal, on colon carcinoma and on breast cancer. The article also gives an overview of the many applications of inulin and oligofructose in the food industry.

Kaur N. & Gupta A.K. (2002). Applications of inulin and oligofructose in health and nutrition. J Biosci, 27, 703-714.

Inulin increases bone mineral density in growing rats

The fact that the addition of inulin to the diet increases calcium (Ca) absorption, does not prove that Ca utilisation in bone is increased during the active growth phase.

In this study, it was investigated whether whole-body bone mineral content (WBBMC), whole-body bone mineral area (WBBA) and whole-body bone mineral density (WBBMD) are increased in healthy growing rats fed diets containing inulin (Raftiline® HP at 0, 5 or 10%) and Ca (0.2, 0.5 or 1%) for 22 weeks. At all ages and at all dietary Ca concentrations, inulin increased WBBMC and WBBMD significantly but not WBBA. The effect of inulin was maximal when its concentration in the diet increased from 0 tot 5%. Increasing Ca intake from 0.2 to 0.5% had no significant effect, whereas increasing it from 0.5 tot 1% did have a significant effect.

The increased Ca accretion in whole-body bones might be due to the previously reported increased intestinal Ca absorption, although a decrease in bone turnover cannot be excluded since Ca absorption was not measured in this study. These data support the hypothesis that increased Ca absorption due to the ingestion of inulin might influence peak bone mass in a positive manner.

Roberfroid M.B., Cumps J. & Devogelaer J-P (2002). Dietary chicory inulin increases whole-body bone mineral density in growing male rats. J Nutr, 132, 3599-3602.

COLOPHON

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AGENDA

Tenerife, Canary Islands

December 5, 2003

Subject: 5th International course of Nutrition, Immunity and Infection

Content: Prebiotics and immune function

Speaker: Nadine JONKERS, ORAFTI

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Paris, France

February 12-13, 2004

Subject: Inulin and Oligofructose - Feelgood Factors for Health and Well-being
4th Orafti Research Conference

Content:
- Inulin and oligofructose as FeelGood Factors
- Inulin and oligofructose and gastrointestinal health and well-being
- Inulin and oligofructose and general health and well-being

Speaker: 24 international scientific experts

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Madrid, Spain

March 24-27, 2004

Subject: X Congreso Ciencia y Tecnologia de los Alimentos

Content: Nutritional benefits of inulin and oligofructose

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Genève, Switzerland

May 11-13, 2004

Subject: Vitafoods 2004

Content: Inulin & oligofructose: Their efficacy as prebiotic fibres in mineral absorption and bone health

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