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Polydextrose in Lipid Metabolism

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1. Introduction

Dietary fiber include fibers from natural sources (such as fruits, vegetables, and wholegrain cereals), fibers that are extracted or obtained by other means from food material, and synthetic carbohydrate polymers, that have been shown to possess physiological health benefits [1, 2]. Dietary fiber can be classified analytically as soluble and insoluble based on their solubility in water, but can also be characterized as viscous or non-viscous and fermentable or non-fermentable depending upon the physiological characteristics the fiber might have [2]. Insoluble dietary fiber includes cellulose, part of hemicellulose, and lignin, whereas soluble fibers include components such as pectin, some hemicelluloses, lignin, gums and mucilage [2, 3]. Whilst there have been difficulties in achieving a global definition for dietary fiber, it is now generally accepted that dietary fiber can be defined as carbohydrate polymers with a degree of polymerization of 3 or more monomeric units which are not hydrolysed in the small intestine by the endogenous enzymes [4]. As fiber is resistant to digestion and absorption in the human small intestine, it enters the colon where it can be partially or completely fermented [5].

Polydextrose is a polysaccharide produced by the random polymerization of glucose in the presence of sorbitol and a suitable acid catalyst, at a high temperature and under partial vacuum [6]. Polydextrose is composed of a mixture of glucose oligomers, with an average degree of polymerization ~12, but ranging from residual monomer to dp >100 [6, 7]. It is a branched molecule, and contains all different combinations of α - and β -linked 1→2, 1→3, 1→4 and 1→6 glycosidic linkages (Figure 1) [7, 8]. As polydextrose is only partially digested during gastrointestinal transit, it acts as a substrate for saccharolytic fermentation throughout the colon, even to the distal parts [9-12]. Polydextrose has a low caloric value: about 1 kcal/g, and it is widely used as a bulking agent and to replace the structure and texture of sucrose in low-calorie products by the food industry in confectionery applications, in pastry and bread, in dairy products, meat products, pasta and noodles, and in beverages [7, 13]. Polydextrose is widely accepted as a soluble fiber and has scientifically substantiated fiber characteristics, including increase in stool weight, decreased transit time, improved

stool consistency and ease of defecation, and reduced fecal pH [7]. It is safe to use, and well tolerated, with a mean laxative threshold of 90 g/day, or 50 g as a single bolus dose [14-16].

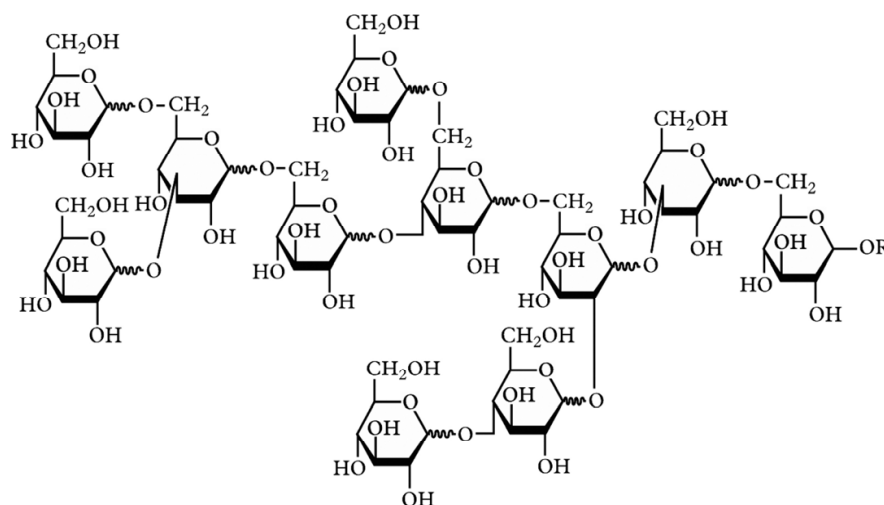


Figure 1. Structure for the polydextrose. The letter R can be either hydrogen (H), sorbitol, sorbitol bridge, or more polydextrose. Polydextrose has highly branched complex three-dimensional structure with all different combinations of α - and β -linked 1 \rightarrow 2, 1 \rightarrow 3, 1 \rightarrow 4 and 1 \rightarrow 6 glycosidic linkages.

Several beneficial effects have been linked to the consumption of polydextrose. Consumption of polydextrose promotes the growth of beneficial bifidobacteria and lactobacilli while preventing the growth of harmful ones, such as clostridia [17, 18]. It has been suggested to possess anti-inflammatory actions and to improve the signs of osteoarthritis in canines [19], to increase IgA amount in the rat cecum [20], to reduce cyclooxygenase 2 expression in pigs distal colon, and to reduce lesions in rat colitis model [21]. Furthermore, it has been suggested to improve the absorption of magnesium, calcium [22-25] and iron [26].

Soluble fiber, both viscous (e.g. gums, pectin and β -glucan) and non-viscous (e.g. polydextrose, resistant maltodextrin and inulin), has been suggested to have beneficial metabolic advantages. These include increasing satiety and reduction of body weight, control of postprandial glycemic and insulin responses, and hypocholesterolemic effects on serum lipid parameters [5, 27]. The inverse relationship of higher HDL to coronary artery disease risk has been recognized and is evident across numerous populations, and the increment of its relative amount over LDL has been generally accepted as a hallmark of better cardiovascular health [28]. Soluble fiber has been associated inversely with serum total and LDL cholesterol, while HDL cholesterol concentration has been reported to either slightly decrease or remain unchanged [29, 30]. This effect has been attributed as an effect of soluble viscous fibers, as insoluble fibers do not appear to affect serum cholesterol concentrations [31, 32]. The ability of soluble fibers to reduce serum triglyceride levels is also controversial, as in some studies an inverse association has been suggested, while in many studies no effect has been observed [29, 33]. Soluble viscous fibers have a characteristic of being hypocholesterolemic, reducing serum cholesterol by about 5-10 % for a 5-10 g dose in subjects with hypercholesterolemia, whereas insoluble fibers have not shown this effect [34].

2. Polydextrose studies in animals, human and *in vitro*: Contribution of polydextrose in lipid metabolism

Polydextrose is a fermentable non-viscous fiber, and has been shown to exhibit lipid metabolism regulating effects [5]. Typically these effects have been associated with two physiochemical properties of soluble fibers: viscosity and fermentability. Viscous soluble fibers may work by slowing down gastric emptying and prevention of bile salt re-absorption which would increase the secretion of bile acids and neutral sterols into feces and interruption of the enterohepatic circulation of bile acids [35, 36]. Soluble fiber can also decrease intestinal cholesterol absorption by affecting micelle formation and mobility [37, 38], and reduce glycemic response leading to lower insulin stimulation and hepatic cholesterol synthesis [39]. Fibers can also promote satiety [40]. Additionally, colonic fermentation products of these fibers, short chain fatty acids (SCFAs), mainly propionate, have been shown to inhibit hepatic fatty acid synthesis [41]. Polydextrose has been reported to confer lipid modulating effects in human clinical intervention studies, as well as in animal studies. However, some of the characteristics of polydextrose are different to other soluble fibers, such as low viscosity, and sustained fermentation throughout the colon [11].

2.1. Polydextrose studies in animals

The ability of polydextrose to modulate triglycerides, total, LDL, and HDL cholesterol has been studied in animals both in normal diets without additional lipid load or in diets in which lipids have been included as part of the normal diet. There is a clear difference between the types of studies, as the two studies without lipid load have not shown any effect on the blood lipid values. In a 6-week feeding study in normal rats with 5 % (w/w) inclusion of polydextrose no change in plasma triglycerides, total cholesterol, and HDL cholesterol or liver cholesterol, triglycerides and phospholipids was observed [42]. Another, 15-day feeding trial with rats, did not show differences in serum total and free cholesterol, triacylglycerols, and phospholipids even though 3 % polydextrose was administered together with 3 % pectin or 3 % cellulose [43].

However, in two other rat feeding studies in which polydextrose was accompanied with a lipid load, reduced lipid levels were reported. In one study rats were given two different dosages of corn oil, 10 % and 20 %, to represent a moderate or high fat diet, for 8 weeks, with or without 5 % polydextrose [44]. Rats in the polydextrose group showed decreased serum triglycerides as compared to a guar gum control in the high-fat diet, and increased levels of serum HDL cholesterol both in the moderate fat and high fat diet [44]. Serum total lipids and cholesterol remained at the level of the control [44]. One study has been done with gerbils: in the 4-week study the gerbils were fed with 0.15 % cholesterol with 30 % of the energy coming from fat and with inclusion of 6 % polydextrose [45]. Both liver and plasma total cholesterol as well as free and esterified cholesterol from liver decreased in the polydextrose group [45]. The effect was presumed by the authors to be related to the reduction of VLDL and LDL, since no change in HDL was observed [45]. In the same gerbil study, it was additionally investigated whether polydextrose can remove cholesterol from

Table 1. Polydextrose studies in relation to lipid metabolism done in animals.

Study design					Cholesterol				
Ref	Animals	Dose	Time	Lipid load	Total	LDL	HDL	TG	Remarks
[42]	Sprague-Dawley rats	5 %	6 w	No load	N.C.	n.a.	N.C.	N.C.	Lipids measured both from plasma and liver
[43]	Sprague-Dawley rats	3 %	15 d	No load	N.C.	n.a.	n.a.	N.C.	Together with pectin or cel-lulosa
[44]	Sprague-Dawley rats	5 %	8 w	10 % and 20 % from corn oil	N.C.	n.a.	↑	↓	Compared to guar gum group
[45]	Gerbils	6 %	4 w	30 % energy from fat, 0.15 % from cholesterol	↓	↓ (or VLDL) ^a	N.C.	N.C.	Liver total ↓, free ↓, esterified cholesterol ↓ Total to HDL ratio trend ↓ in plasma
[45]	Gerbils	6 %	3 w	0.4 % cholesterol preload ^b	↓	n.a.	↓	N.C.	Liver total ↓, Esterified cholesterol ↓
[46]	Wistar rats	28 % as 3 ml/200 g body weight	Acute	Fats as in chocolate	n.a.	n.a.	n.a.	↓	Together with 25.7 % lactitol

n.a. not available; d days; w weeks; m months; a ↓reduced; ↑increased; Trend ↓or Trend ↑only a tendency for reduced or increased values were observed; N.C. no change

^aIndirect evidence, LDL and VLDL were not directly measured but authors concluded that as total cholesterol decreased and there was no change in HDL, then preferential target is then VLDL and/or LDL.

^b0.4 % cholesterol administered to the gerbils 2 weeks prior the feeding with polydextrose in order to expand the endogenous cholesterol pools.

^c0.4 % cholesterol administered to the gerbils 2 weeks prior the feeding with polydextrose in order to expand the endogenous cholesterol pools.

endogenous pools by first artificially expanding the endogenous cholesterol pools of the gerbils with a preload of 0.4 % cholesterol for two weeks before 6 % polydextrose was fed for an additional three weeks. Polydextrose was shown to hasten the endogenous clearance of cholesterol pools, and to reduce liver and plasma total cholesterol, esterified cholesterol from liver and plasma HDL cholesterol [45].

The acute response of polydextrose on serum lipid values has also been studied in rats, but together with lactitol [46]. Polydextrose was administered as a 28 % solution in a dose of 3 ml/200 g of body weight in a solution also containing 26 % lactitol and a fat emulsion which was comparable to one in chocolate. The rats showed reduced serum triglyceride levels, and an increase in luminal triglyceride levels in the cecum after 150 minutes of ingestion of polydextrose, which would indicate that the combination of polydextrose and lactitol reduced either the level of fat absorption in the earlier part of small intestine or promoted the transit time of fat through the intestine [46]. No change in total, HDL, or LDL cholesterol were found in that study.

These studies are summarised in Table 1. There is an indication from these studies that polydextrose can lower total cholesterol and has a tendency to lower LDL cholesterol and tendency to increase HDL cholesterol.

2.2. Polydextrose lipid metabolism studies in clinical intervention studies

Clinical intervention studies with polydextrose have been conducted either with healthy adults, with individuals having hypercholesterolemia or with individuals with impaired glucose tolerance.

In a human study with normal healthy adults with no reported hypercholesterolemia a reduction in the amount of total HDL by administration of 15 g of polydextrose for two months with concomitant decrease in apolipoprotein A-I, which is the main component of the HDL cholesterol, has been observed [47]. Apolipoprotein B levels, found in all atherogenic apolipoprotein particles, and the LDL cholesterol levels itself had also a tendency to be reduced after the 2-month and 1-month intervention period, respectively [47]. In another study with healthy adults, administration of 10 g of polydextrose for 18 days was shown to decrease LDL cholesterol and total cholesterol values with no effect on HDL cholesterol or triglycerides [48]. There are also contradictory results with healthy humans, as administration of polydextrose in an amount from 4 to 12 g per day for 29 days did not affect triacylglycerol, or cholesterol [49]. However, in that study no data was shown, and in addition to which the cholesterol type measured was not specified.

In hypercholesterolemic individuals, the effect of polydextrose has been studied in a 4-week study with administration of 15 g and 30 g polydextrose daily [45]. The study was quite small, with only 12 subjects participating, and each individual subject serving as a control for him/herself. In this study it was noted that 5 of the 6 individuals ingesting 30 g of polydextrose were in a separate responder group, and in this group the LDL cholesterol values declined significantly, and there was a tendency for reduced total cholesterol, but no change in HDL cholesterol. However, when all 6 individuals were studied together, no change compared to control was observed.

In diabetic patients, diets containing high amounts of fiber have improved plasma lipid control [50, 51]. The effect of polydextrose on lipid values has been of interest in two studies with individuals showing abnormal glucose metabolism or type 2 diabetes. In subjects with impaired glucose metabolism, polydextrose administered for 12 weeks at 16 g/day has been observed to lower LDL cholesterol, increase HDL cholesterol and cause no change in triglycerides [52]. In this study, LDL cholesterol decreased also in the control group probably because of simultaneous nutrition consultation by a nutritionist [52]. In a combination study with 7 g polydextrose and 3 g oligofructose administered daily for 6 weeks in adults with type 2 diabetes, a decrease in total cholesterol, triglycerides, VLDL cholesterol, and ratios of total cholesterol to HDL cholesterol, and LDL cholesterol to HDL cholesterol was observed, while HDL cholesterol increased [53].

The acute effect of polydextrose has been studied in humans too, together with lactitol, in the triglyceride levels after consumption of 46 g of chocolate supplemented with 15.1 % of the weight with polydextrose. The intervention group had reduced serum triglycerides in comparison to control chocolate during the 150 minutes the triglycerides were measured from the blood [46]. During intense exercise, polydextrose has been shown to reduce the amount of free fatty acids in plasma [54]. In addition, an abstract has been published about ingestion of 12.5 g polydextrose during a hamburger meal observing a reduction in total postprandial hypertriglyceridemia by 25 % [55].

2.2.1. Effect of polydextrose on different HDL subfractions

HDL is highly heterogeneous, and subfractions of it can be identified on the basis of density, size, charge, and protein composition [56]. Different fractions of HDL can be identified by ultracentrifugation, gradient gel electrophoresis, and nuclear magnetic resonance (NMR) spectroscopy, and these different fractions could play diverse roles in protective function [56, 57]. It is thought that certain fractions of HDL cholesterol could be better predictors of cardiovascular diseases and its risk. However, controversy about the role of the different forms still exists, as in [58] and in [59] increased HDL2 and apoA-I levels were associated as protective against coronary heart disease. In other studies, in turn, such as in [60], and [61], the HDL3 has had a stronger inverse association with coronary heart disease. The early studies, however, more strongly indicate that reduced levels of HDL2 over HDL3 is associated more strongly to CVD risk [62].

The different subfractions of HDL and the impact of ingestion of polydextrose on their distribution has been investigated in one study [47], and in this study HDL3 was increased during the 2-month intervention period and one month after finishing the study. At the same time, a reduced level of HDL2, apoA-I and LCAT activity was observed. In other studies with soluble fibers, such as with guar gum, no changes in HDL2 and HDL3 subfractions or their ratio were observed [63, 64]. No difference between serum HDL2 and HDL3 cholesterol subfractions could be observed between high-fiber, consisting partially of soluble fiber from psyllium, and low-fiber diets [65] or with beta-glucan as an oat fiber extract [66]. In addition, lack of standardization among the analytical methods that are used to measure size distribution of different HDL2 and HDL3 subfractions may cause approximation of HDL subclass levels [67, 68].

Table 2. Polydextrose clinical intervention studies in which lipid values have been measured.

Study design					Cholesterol				
Ref		Dose	Time	Lipid load	Total	LDL	HDL	TG	Remarks
[47]	Healthy	15 g/day	2 m		N.C.	N.C. ^a	HDL2↓ HDL3↑	N.C. ^a	ApoA-I ↓ ApoA-II ↓
[69]	Healthy	15 g/day	4 w		Trend↓ ^b	Trend↓ ^b	N.C.	N.C.	ApoB ↓
[48]	Healthy	10 g/day	18 d		↓	↓	N.C.	N.C.	
[49]	Healthy	4, 8, or 12 g/day	28 d		N.C.	N.C.	N.C.	N.C.	Measured lipid values were not specific
[46]	Healthy	15.1 % in 46 g of chololate	Acute	Lipids from chocolate	n.a.	n.a.	n.a.	↓	Together with 19.4 % lactitol
[45]	With hypercholesterolemia	15 or 30 g/day	4 w		Trend ↓ ^c	↓ ^c	N.C. ^d	N.C. ^d	
[52]	With impaired glucose metabolism	16 g/day	12 w		N.C.	↓	↑	N.C.	Total to HDL ratio ↓
[53]	With type 2 diabetes	13.2 g/day	6 w		↓	↓	↑	↓	With 6.8 g oligofructose/day. Total/HDL cholesterol ↓, VLDL cholesterol ↓

n.a. not available; d days; w weeks; m months; ↓reduced; ↑increased; Trend ↓or Trend ↑only tendency for reduced or increased values were observed; N.C. no change

^a had a tendency to be reduced 1 month after intervention

^b Total cholesterol and LDL cholesterol were reduced by 6 % but not significantly

^c When studied form a group that responded to the 30 daily dose of polydextrose

^d Both in the responder group that ingested 30g/day polydextrose and in a group in which in addition to responders, a non-responder was included.

Table 2 summarizes the different human clinical intervention studies done with polydextrose in relation to HDL, LDL, total cholesterol and triglycerides. From these studies it can be concluded that polydextrose in the diet can lower serum total and LDL cholesterol and triglycerides. There are two studies in which definite increases in HDL have been observed.

3. Mechanisms for polydextrose action on lipid values

3.1. Role of polydextrose in enterohepatic bile circulation and in cholesterol absorption

One of the mechanisms by which soluble viscous fibers induce hypocholesterolemic responses is the disruption of enterohepatic bile acid circulation, which reduces absorption of intestinal bile acids. The major route by which cholesterol in the liver is eliminated is through the de novo synthesis of primary bile acids from cholesterol [70]. The bile is released into the small intestine, where bile salt micelles help in the solubilisation of lipophilic components, such as cholesterol, fat soluble vitamins, and other lipids [70]. The diffusion of the micelles with solubilised components as well as the biliary and dietary cholesterol across the unstirred water layer, covering the luminal side of the enterocytes facilitate the uptake of cholesterol and other lipophilic components by the enterocytes [71]. When the bile salt micelles have accomplished their role they transit the remainder of small and large intestine where they are progressively absorbed into the enterohepatic circulation by the hepatic portal vein [70]. The bile salts that escape the intestinal absorption are transformed through colonic bacterial enzymatic activity to form secondary bile salts, from which deoxycholic acid is absorbed passively through colonic epithelium into the enterohepatic circulation, while lithocholic acid is secreted into the feces [72]. The amount of bile salts, both primary and secondary, is maintained in a rather constant level, and the daily bile salt losses are compensated by de novo hepatic biosynthesis [73]. The enterohepatic circulation is very efficient, as 95 % of the bile salts released into the intestine is absorbed back to the liver [70].

The presence of viscous soluble fiber has been shown to prevent bile salt reabsorption, which leads to enhanced excretion of bile salts into feces [35, 36]. This depletes the bile acids from liver and leads to rapid catabolisation of cholesterol through activation of 7 α -hydroxylase. At the same time cholesteryl esters are metabolised, and in order to replace these production of LDL surface membrane receptors and concomitant LDL cholesterol uptake from blood stream are increased. This leads to lowering of the blood cholesterol concentration [74]. The fibers presumably interact with bile acids directly at the molecular level or entrap bile salt micelles in the gelatinous network formed by the polymeric fiber [35, 75]. The fiber can also form a barrier which can prevent the formation of bile acid micelles, and increase the unstirred water layer lining the intestinal mucosal surface [76].

Polydextrose is a non-viscous fiber and its capacity to bind bile salts has been studied in one clinical intervention study [77]. In this study, administration of polydextrose in healthy

adults at 8 g/day for three weeks was not found to increase fecal excretion of total bile acids and secondary bile acids, but rather decreased values were observed during the intervention period compared to the run-in period before [77]. A similar observation was made in normal rats, in which administration of 5 % polydextrose for 6 weeks did not increase the fecal output of bile acids [42]. The low ability of polydextrose to bind bile acids is not, however, surprising. In order for a fiber to bind bile acids, it is required to be viscous in nature, and polydextrose is lower in viscosity for instance in comparison to pectin and guar gum which have high water binding capacity with higher viscosity and thus increased capability to bind bile acids [42, 78]. Polydextrose has a high capacity to bind water, and it can for instance relieve constipation presumably due to this characteristic, but there is no gel formation by polydextrose in water and little viscosity [43, 79, 80].

Even though no clear effect on bile acid binding can be detected, the fact that cholesterol and triglyceride absorption can still be modulated, are indications that polydextrose can retard the transportation of lipids from the intestinal lumen to the lymph. When polydextrose was infused as 5 % and 10 % to duodenum together with cholesterol and triglyceride on mesenteric lymph-fistulated rats, the amount of cholesterol and triglycerides in the lymph decreased dose-dependently, and concomitantly the amount of the unabsorbed lipids increased in the lumen of the intestine [81]. It was concluded that since most of the luminal triglyceride and cholesterol was detected in the proximal part of the small intestine, the absorption of the lipids was inhibited. There was a tendency to have increased amount of cholesterol and a significant increase of triglycerides remaining in the colon which could indicate that some of the lipids were not absorbed [81]. However, polydextrose did not seem to increase secretion of cholesterol into feces in rats even though some tendency was observed in another study [82].

In an acute response study of polydextrose in combination with lactitol in rats with lipid load similar to the composition of chocolate an increase in luminal triglyceride in the cecum was observed with concomitant decrease in serum triglycerides [46]. This would indicate that the combination of polydextrose and lactitol reduced either the level of fat absorption in the earlier part of small intestine or promoted the transit time of fat through the intestine [46].

Cholesterol that escapes absorption is partially degraded to coprostanol and coprostanone by colon microbes [83]. A decrease of the degradation products coprostanol, coprostanone and cholestanol has been observed [77] which would indicate that the amount of cholesterol entering the colon is less in humans receiving polydextrose.

3.2. Role of polydextrose on intestinal microbiota and its impact on cholesterol metabolism

When soluble fiber enters the large intestine, it is fermented by the residual microbes forming short-chain fatty acids (SCFAs), butyrate, acetate, and propionate, end-products of

bacterial carbohydrate fermentation. The SCFAs have been indicated to possess different physiological functions. Butyrate has been implicated to be the most important SCFA for colonic and immune cells due to its ability to serve as energy source for colonic epithelium as well as regulate cell growth and differentiation [84, 85]. It is a preferred energy source by colonocytes over glucose, glutamine, or other SCFA, and 70 to 90 % of butyrate is metabolized by colonocytes [86]. It has been implicated to inhibit intestinal cholesterol biosynthesis [87]. Acetate, as a direct substrate for acetyl-CoA synthetase, an enzyme that converts acetate to acetyl-CoA for entering to the cholesterol and fatty acid synthesis cycle, has been implicated to increase liver cholesterol, and fatty acid levels [41, 88]. Acetate has been shown to associate negatively with visceral adipose tissues and insulin levels in obese people [89]. Propionate has been shown to possess antilipogenic and cholesterol-lowering effects. While acetate is a substrate for sterol and fatty acid synthesis, propionate counteracts this by inhibiting acetate incorporation to serum lipids [41]. Propionate has been shown to reduce the rate of cholesterol synthesis [87, 90], to inhibit fatty acid synthesis [91], to decrease liver lipogenesis [92], and to decrease hepatic and plasma and serum cholesterol levels [93, 94]. Propionate supplementation has been shown increase serum HDL cholesterol and triglyceride levels without effect on total cholesterol [92, 95]. However, contradictory results about its efficacy on cholesterol metabolism has been also observed [96-98].

The production of short-chain fatty acids during polydextrose fermentation has been studied with batch fermentations, colon simulators as well as from feces in animal and human studies. The differences in the results reflect individual variation, sampling, and differences in the methods used. Fecal SCFA concentration measurements are not the best indicators of SCFA produced as the majority of fecal SCFA is absorbed rapidly by the colonic epithelial cells [99]. Polydextrose has been observed to increase the production of butyrate, acetate and propionate in vitro [18, 100-102], in rats [20], pigs [11], in dogs [103] and in humans [17, 49]. When compared to other fibers, polydextrose produced similar quantities of SCFAs, and the molecular ratio of acetate/propionate/butyrate produced was found to be similar to that of fructo-oligosaccharides and xylo-oligosaccharides and other carbohydrates, such as inulin, pectin, and arabinose [104, 105] while in other studies polydextrose produced less total SCFAs compared to FOS, inulin and GOS [102, 106, 107]. The lower production of SCFAs by polydextrose can be explained by the lower digestability of polydextrose and its more sustained fermentation throughout the gut due to its branched complex structure. Furthermore, polydextrose fermentation has been shown to reduce putrefactive microbial metabolites, or branched-chain fatty acids and biogenic amines produced from protein fermentation [11, 20, 49, 100, 101, 107-109] but the decrease of these in relation to lipid metabolism and absorption is unknown. Figure 2 shows an example of how fermentation of polydextrose increases the amount short chain fatty acids in an in vitro colon simulation both when the amount of polydextrose is increased, and when the simulation proceeds from vessel V1 representing proximal part of the colon towards the vessels representing more distal parts of the colon [108].

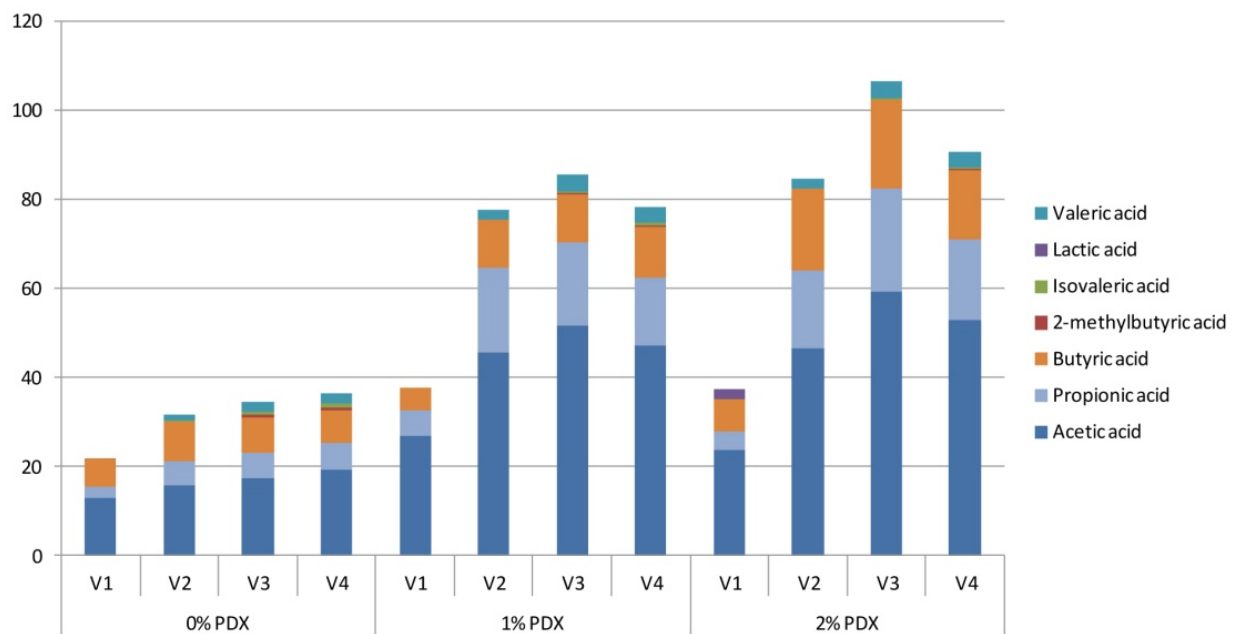


Figure 2. Concentration (mM) of short chain fatty acids (SCFAs) in the different vessels V1, V2, V3, and V4 after 48h in vitro colon fermentation simulation. An increase in the concentration of SCFAs can be observed both dose-dependently as well as from vessels representing proximal colon V1 towards vessels representing more distal parts of the colon, V3 and V4.

When polydextrose enters the colon, it is fermented by the indigenous microbiota, thus serving as an energy-source to promote their growth and survival. In germ-free mice, the transplantation of the colonic microbiota from normal mice resulted in a 60 % increase in body fat in an unchanged diet [110] and there are an increasing number of reports that the gut microbiota may play an important role in cholesterol and lipid homeostasis, in obesity and metabolic syndrome [111-113].

Bacterial DNA of fecal samples from 20 individuals consuming 21 g of polydextrose in 3 doses per day were pyrosequenced, and the amount of Clostridiaceae, and Veillonella increased while Lachnospiraceae and Eubacteriaceae decreased compared to the control group without additional supplemental fiber [114]. Well-known butyrate-producers were increased in number, such as Faecalibacterium, and especially Faecalibacterium prausnitzii, whereas other SCFA producers, such as Lachnospiraceae, and Eubacteriaceae were reduced in number by administration of polydextrose [114]. Polydextrose also decreased the number of Coriobacteriaceae, which have been shown to have a positive association to non-HDL cholesterol [111, 114]. Interestingly, bifidobacteria have shown a positive correlation with HDL-cholesterol [111], but the bifidobacterial counts were decreased by polydextrose when studied with pyrosequencing [114]. In other studies polydextrose administration has been shown to increase the amount of bifidobacteria and lactobacilli [17, 18, 49, 106, 107, 115] while in some studies this effect has not been noted [103] or that there was no effect on the growth of lactobacilli [102]. This kind of inconsistency in the response could reflect the interindividual differences in indigenous microbiota to begin with. These kind of fluctuations in the indigenous microbiota, however, might explain why there are

differences in the studies with polydextrose and its effect on cholesterol values, for instance in [45] in which a responder group with a decrease in LDL was observed.

3.3. Polydextrose effect on glycemic control and insulin response

Fibers can affect blood glucose levels by decreasing the glycemic load of a meal or by affecting glucose absorption or release of glucose [5], and especially soluble fiber has been shown to attenuate the absorption of glucose [27]. Soluble dietary fibers may affect total and LDL cholesterol levels through effects on postprandial glycemia, as reduction in the glucose absorption, which would lower the insulin level and its production in the pancreas, would then lead to a decrease in cholesterol synthesis [116]. When soluble dietary fibers are being digested they delay the emptying of digested food from the stomach to the small intestine, slow down the transportation and mixing of digestive enzymes in the chyme and increase the resistance of the unstirred water layer lining the mucosa [117, 118]. This leads to reduction in the absorption of glucose and macronutrients, and lowered level of postprandial glucose is accompanied with lowered insulin level which would possibly lead to lowered hepatic cholesterol synthesis. [39]. There has been studies describing inverse relationship between glycemic load and HDL cholesterol [119, 120], and an indirect regulation of intestinal lipid uptake by dietary glucose has been presumed. Short-term incubation with intestinal epithelial cells, Caco-2 cells, with glucose on the apical side induces a significant uptake of cholesterol in a dose-dependent manner [121], and in addition cholesterol synthesis seems to depend on glucose intake [122].

The effect of polydextrose ingestion on glucose and postprandial insulin response has been investigated in several studies. Polydextrose has a very low glycemic index (4 to 7) with glycemic load of 1 compared to the reference glucose (100) [7, 123]. Polydextrose has been reported to attenuate the blood glucose raising potential of glucose, as the glycemic index of glucose was reduced from 100 to 88 when 12 grams of polydextrose was ingested together with glucose by healthy adults [49]. Similar results were observed in a study with healthy adults when 14 g was ingested together with 50 g of glucose or 106 g of bread [124]. Plasma glucose levels were decreased by 28 % and 35 %, compared to glucose and bread without polydextrose, respectively, with significantly reduced serum insulin levels in the glucose plus polydextrose group [124]. These observations indicate that polydextrose could reduce the absorption of glucose. When the effect of polydextrose was studied with human subjects with impaired glucose tolerance or impaired fasting glucose, no change in plasma glucose or insulin has been observed [52]. However, this study [52] had a moderately high fructose intake which could have affected the results as fructose does not induce endogenous secretion of insulin [125]. Diurnally polydextrose did not seem to change plasma sugar levels, but a decrease in insulin after meals was noted [69]. In dogs, polydextrose showed an attenuated postprandial glycemic and lower relative insulin responses than the control sugar maltitol [126].

Polydextrose has been also studied in trials in which the reference group received a normal meal/snack with glucose, and the intervention group the same but with the glucose partially

replaced with polydextrose. In volunteers with type 2 diabetes, cranberries with 10g of polydextrose showed attenuated plasma glucose and insulin response compared to cranberries with glucose [127]. In one study with healthy adults, significantly lower postprandial glucose levels were observed after ingestion of strawberry jam with 40 % polydextrose than after ingestion of strawberry jam sweetened with sugar, corn syrup, or apple juice, but this study did not measure insulin [128].

These above results indicate that polydextrose might have a role in postprandial glucose absorption and insulin response. One good candidate to modify insulin response is again the SCFAs, especially propionate, which have been shown to improve insulin sensitivity during glucose tolerance tests [95]. Polydextrose also might interfere the release and absorption of the glucose in the small intestine which would lead to slower and lower blood sugar rise [5]. In some of these studies the response is observed because polydextrose was used as sugar substitute to lower the caloric content of the snack/product [127, 128]. In [127] the beneficial insulin reduction was observed not to be in 1:1 ratio with caloric reduction so there might be additional beneficial effect apart from lowering the overall calorie content.

3.4. Polydextrose as a satiety increasing agent

Meals dense in fiber have also been demonstrated to be able to control the sense of hunger, satiety, inhibit the desire for another meal, or induce satiation, limit the size of the meal, possibly by lowering caloric density or slowing down gastric emptying [40, 129] This would further decrease the sugar load of the individual, since high-fiber diets usually have a lower glycemic load.

Polydextrose has been observed to significantly reduce the feeling of hunger in subjects with impaired glucose metabolism [52], and to have tendency towards reduced snacking [10]. It has been shown to increase satiety and to reduce food intake when combined with yoghurt preloads [130]. However, evidence has been conflicting - in one study when 25 g polydextrose was preloaded in two servings before lunch, no difference in the desire to eat, sense of hunger and fullness was observed between polydextrose and the other fibers tested [131]. In this study polydextrose did not decrease the energy consumed in lunch. In another study when polydextrose was consumed as 9.5 g in a muffin no difference in the feeling of hungriness or food intake was observed between polydextrose and the other fibers studied [132]. In the two most recent studies, polydextrose intake of 12 g in a fruit smoothie, consumed as a single dose preload, significantly reduced the intake of energy in a buffet lunch 1 hour after the consumption of the smoothie [133]. Similar observations with a single dose of 6.25 g or 12.5 g of polydextrose before a test lunch were also made in another study [134, 135].

Both butyrate and propionate have been shown to induce gut hormones and reduce food intake [136]. Propionate has been shown to act as a satiety-inducing agent, with strong effects on energy intake and feeding behaviour with significantly greater feeling of fullness and lower desire to eat [137, 138]. This could be introduced by the modulation of the colonic mucosa secreted peptide hormones that regulate appetite, such as glucagon like peptide -1

(GLP-1), peptide YY (PYY), oxyntomodulin, or SCFA receptors, GPR43 or GPR41, which have been localized in intestinal enteroendocrine L cells, that are responsible for the production of the appetite regulating hormones [139, 140] but whether polydextrose ingestion causes changes in these peptide hormones remains to be investigated.

3.5. Modulation of genes regulating energy metabolism by polydextrose fermentation in colon

Microbial metabolites have been shown to modulate gene expression, for instance butyrate acts as a histone deacetylase (HDAC) inhibitor, and affects gene transcription [141]. Polydextrose has been shown to increase expression of PPAR γ in the colon of mice [142]. This has been attributed to be mediated at least by butyrate, which can not only up regulate gene expression of PPAR γ , but also activate it [143]. When intestinal epithelial cells were treated with polydextrose fermentation metabolites, a gene expression signature was induced that approached the response of butyrate [144]. In the study [144] 1 or 2 % polydextrose was fermented in a four-stage semicontinuous colon simulation model, in which each vessel in sequence represents different parts of the colon. Caco-2 cells were treated with the polydextrose fermentation metabolites from each vessel, and the idea was to analyse gene expression pattern of the Caco-2 cells treated with fermentation metabolome representing the whole colon. The weakness of this study was that the cells were not differentiated, but were used as a cancer cell model, and that fermentation metabolites originated from a fecal sample only from one individual. In the gene ontology analysis of this study, enrichment of class "lipid metabolism" by the polydextrose fermentation metabolites was noted, which indicated that genes involved in energy metabolism were regulated. Indeed, induction of PPAR α , PGC-1 α , and Lipin 1 which are major regulators of the metabolism, were observed. Additionally, some PPAR α responsive genes were observed to be up regulated, such as SORBS1, LPIN1, NPC1, FATP1, HMOX1, and ACSL1 [144].

In the intestine, activation of PPAR α results in the specific induction of genes involved in fatty acid uptake, binding, transport, and catabolism. In addition, genes involved in triacylglycerol and glycerolipid metabolism have been suggested to function as fatty acid sensors, and in nutrient absorption [145, 146]. PGC-1 α participates to the regulation of both carbohydrate and lipid metabolism, and it has been involved in the adaptation of and maintenance of energy homeostasis in caloric restriction [147]. *Drosophila* PGC-1 α homolog increases mitochondrial gene expression and activity and protects against age-related loss of intestinal homeostasis and integrity, and is suggested to extend life span [148]. Lipin 1 is induced by PGC-1 α in liver and acts to amplify PGC-1 α and to activate many of the genes of mitochondrial fatty acid oxidative metabolism [149]. Lipin 1 has been associated with insulin sensitivity in adipose tissue and liver which indicates that it has a profound role in maintaining systemic metabolic homeostasis [150, 151].

One of the genes regulated by polydextrose fermentation metabolites was Niemann Pick C1 (NPC1), a significant contributor to plasma HDL cholesterol formation [152]. NPC1 facilitates the movement of cholesterol to ABCA1, a cholesterol transporter that is located in

the basolateral membrane of enterocytes, that is involved in the efflux process of cholesterol to circulating HDL particles [153]. Approximately 30 % of the steady-state HDL was contributed by the intestinal ABCA1 in mice [154]. In NPC1 deficient cells the HDL cholesterol formation is reduced [155].

4. Conclusions

Based on the current research there is clear evidence that polydextrose has the ability to attenuate glucose absorption, reduce insulin response and lower blood LDL, total cholesterol and triglyceride levels. HDL cholesterol shows a tendency to be increased, but this has not been consistently demonstrated in all studies. This kind of ability to increase HDL would be quite unique among soluble fermentable fibers. Animal studies also indicate that polydextrose could interfere with cholesterol and triglyceride absorption.

Figure 3 summarises the possible mechanisms of how polydextrose could affect cholesterol and lipid metabolism. Polydextrose is used as a bulking agent, and increases the bulk of the material that transits along the colon. This can provide a sense of fullness and satiety. The effect of polydextrose on bile acid secretion cannot be definitely concluded at this point but is unlikely due to its non-viscous characteristic. It seems, that polydextrose attenuates the blood glucose raising potential of glucose itself, and the insulin response. Glucose and insulin are linked to hepatic de novo cholesterol synthesis, cholesterol absorption and HDL formation. The mechanism of the lipid metabolism modulating effect of polydextrose might be indirect, through its fermentation by the indigenous microbiota either the luminal or mucosal, that at the same time increase SCFA production. The microbiota can affect cholesterol degradation, but could also for instance affect chylomicron formation and cholesterol absorption. The absorbed SCFAs, propionate and butyrate, are linked to diminishing de novo cholesterol synthesis in the liver. Acetate, in contrast, has an opposite effect. Whether SCFAs are the molecules exerting the effect of the polydextrose is not known. During the fermentation of soluble fibers other metabolites apart from SCFAs are formed [156]. The complex structure of polydextrose facilitates its fermentation throughout colon. This differentiates it from other fibers which are fermented early in the colon, and it serves as an energy source for bacteria throughout the colon, and changes in the composition of the microbiota are observed with an increase in butyrate-producing bacteria [114]. It is possible that due to its fermentation characteristics the long-term effect on microbiota composition might be different to other soluble fibers. The mechanism of polydextrose might also be direct, through modulation of surface receptors, but currently there is no evidence for this.

The microarray study has given ideas of how polydextrose fermentation metabolites might affect the intestinal tissue. The evidence is, however, at the transcriptional level only, and is speculative. Additional studies in the possible regulation of PPAR α , PGC1 α , Lipin1, NPC1, and others by polydextrose is thus needed. In vitro studies could be used for instance to study the role of polydextrose fermentation in HDL formation using a differentiated Caco-2 cell model which has shown to be good model to study de novo ApoA-I production [157].

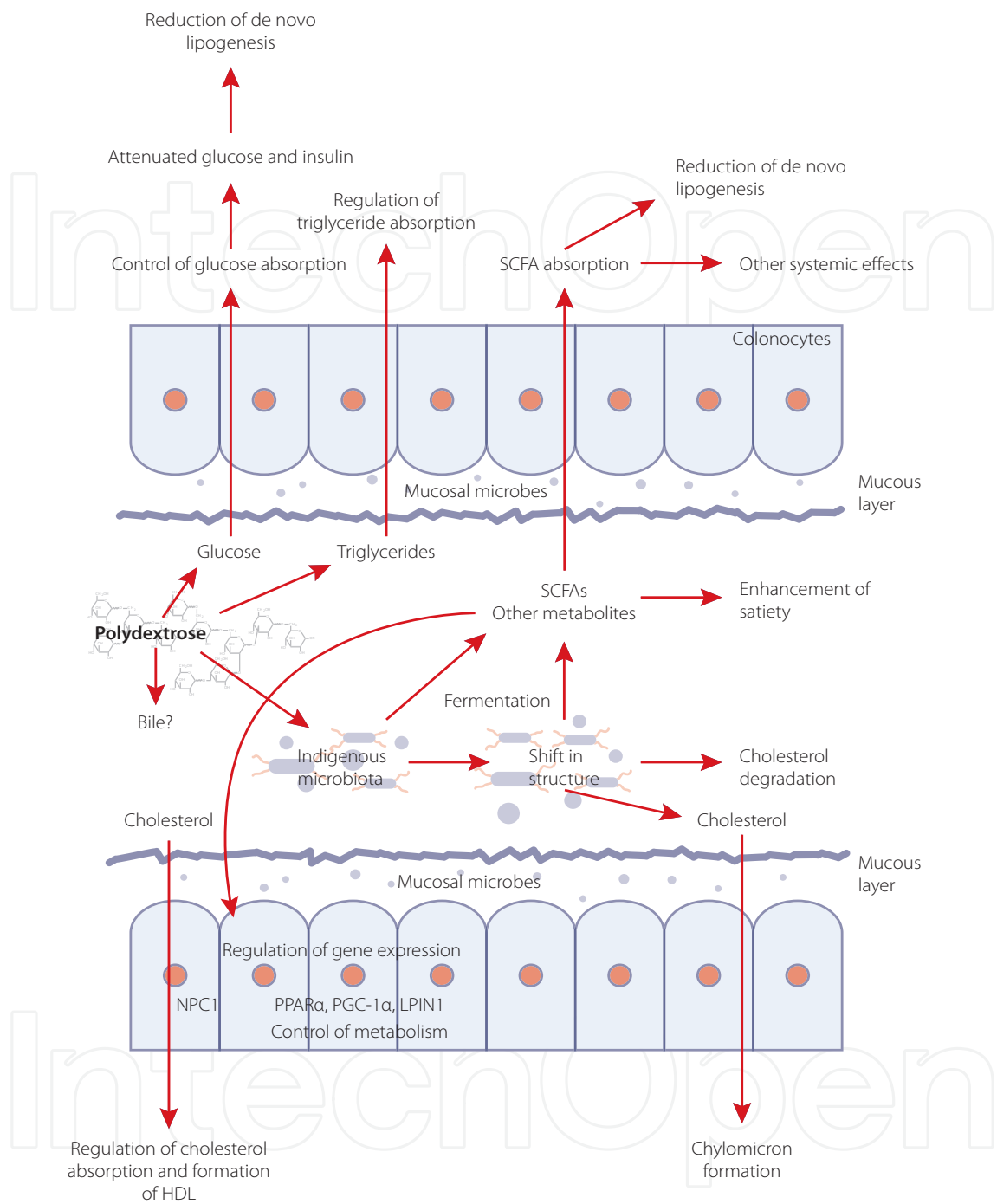


Figure 3. Summary of the polydextrose function in lipid metabolism.

It could be worthwhile to investigate to what extent polydextrose fermentation metabolites cause systemic effects for instance in liver, and its de novo cholesterol synthesis, not forgetting the role of the intestine. When lipidemic conditions are normal, the liver is the most important site of cholesterol biosynthesis, followed by the intestine. Biosynthesis in the liver and intestine account for about 15 and 10 %, respectively, in the total amount of cholesterol biosynthesis each day [158] [159]. In hypercholesterolemia, when cholesterol

biosynthesis is suppressed in most organs by fasting, the intestine becomes the major site of cholesterol biosynthesis, and its contribution can increase up to 50 % [160, 161]. Mixtures of short chain fatty acids have been shown to suppress cholesterol synthesis in the rat liver and intestine [162], and whether fermentation metabolites from polydextrose can inhibit cholesterol biosynthesis in the intestine, or even in the liver, is an open question.

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5. References

- [1] Phillips GO, Cui SW. An Introduction: Evolution and Finalisation of the Regulatory Definition of Dietary Fibre. *Food Hydrocolloids* 2011;25 (2) 139-143.
- [2] DeVries JW, Camire ME, Cho S, Craig S, Gordon D, Jones JM, Li B, Lineback D, Prosky L, Tunland BC. The Definition of Dietary Fiber. *Cereal Foods World* 2001;46 (3) 112-129.
- [3] Roberfroid M, Gibson GR, Hoyle L, McCartney AL, Rastall R, Rowland I, Wolvers D, Watzl B, Szajewska H, Stahl B, Guarner F, Respondek F, Whelan K, Coxam V, Davicco MJ, Leotoing L, Wittrant Y, Delzenne NM, Cani PD, Neyrinck AM, Meheust A. Prebiotic Effects: Metabolic and Health Benefits. *British Journal of Nutrition* 2010;104 (S2) S1-S63.
- [4] Howlett JF, Betteridge VA, Champ M, Craig SAS, Meheust A, Jones JM. The Definition of Dietary Fiber - Discussions at the Ninth Vahouny Fiber Symposium: Building Scientific Agreement. *Food and Nutrition Research* 2010;54 (1)
- [5] Raninen K, Lappi J, Mykkänen H, Poutanen K. Dietary Fiber Type Reflects Physiological Functionality: Comparison of Grain Fiber, Inulin, and Polydextrose. *Nutrition Reviews* 2011;69 (1) 9-21.
- [6] Craig SAS, Holden JF, Troup JP, Auerbach MH, Frier HI. Polydextrose as Soluble Fiber: Physiological and Analytical Aspects. *Cereal Foods World* 1998;43 (5) 370-376.
- [7] Stowell JD. Polydextrose. In: Sungsoo S, Samuel P (ed.) *Fiber Ingredients, Food Applications and Health Benefits*, Boca Raton: CRC Press; 2009. p173-201.
- [8] Stumm I, Baltes W. Analysis of the Linkage Positions in Polydextrose by the Reductive Cleavage Method. *Food Chemistry* 1997;59 (2) 291-297.
- [9] Achour L, Flourie B, Briet F, Pellier P, Marteau P, Rambaud JC. Gastrointestinal Effects and Energy Value of Polydextrose in Healthy Nonobese Men. *American Journal of Clinical Nutrition* 1994;59 (6) 1362-1368.

- [10] Costabile A, Fava F, Röytiö H, Forssten SD, Olli K, Klievink J, Rowland IR, Ouwehand AC, Rastall RA, Gibson GR, Walton GE. Impact of Polydextrose on the Faecal Microbiota: A Double-Blind, Crossover, Placebo-Controlled Feeding Study in Healthy Human Subjects. *British Journal of Nutrition* 2011;111:1-11.
- [11] Fava F, Makivuokko H, Siljander-Rasi H, Putaala H, Tiihonen K, Stowell J, Tuohy K, Gibson G, Rautonen N. Effect of Polydextrose on Intestinal Microbes and Immune Functions in Pigs. *British Journal of Nutrition* 2007;98 (1) 123-133.
- [12] Lahtinen SJ, Knoblock K, Drakoularakou A, Jacob M, Stowell J, Gibson GR, Ouwehand AC. Effect of Molecule Branching and Glycosidic Linkage on the Degradation of Polydextrose by Gut Microbiota. *Bioscience Biotechnology and Biochemistry* 2010;74 (10) 2016-2021.
- [13] Auerbach MH, Craig SAS, Howlett JF, Hayes KC. Caloric Availability of Polydextrose. *Nutrition Reviews* 2007;65 (12) 544-549.
- [14] Flood MT, Auerbach MH, Craig SAS. A Review of the Clinical Tolerant Studies of Polydextrose in Food. *Food and Chemical Toxicology* 2004;42 (9) 1531-1542.
- [15] Burdock GA, Flamm WG. A Review of the Studies of the Safety of Polydextrose in Food. *Food and Chemical Toxicology* 1999;37 (2-3) 233-264.
- [16] Herfel TM, Jacobi SK, Lin X, Walker DC, Jouni ZE, Odle J. Safety Evaluation of Polydextrose in Infant Formula Using a Suckling Piglet Model. *Food and Chemical Toxicology* 2009;47 (7) 1530-1537.
- [17] Beards E, Tuohy K, Gibson G. A Human Volunteer Study to Assess the Impact of Confectionery Sweeteners on the Gut Microbiota Composition. *British Journal of Nutrition* 2010;104 (5) 701-708.
- [18] Beards E, Tuohy K, Gibson G. Bacterial, Scfa and Gas Profiles of a Range of Food Ingredients Following in Vitro Fermentation by Human Colonic Microbiota. *Anaerobe* 2010;16 (4) 420-425.
- [19] Beynen AC, Saris DHJ, de Jong L, Staats M, Einerhand AWC. Impact of Dietary Polydextrose on Clinical Signs of Canine Osteoarthritis. *American Journal of Animal and Veterinary Sciences* 2011;6 (3) 93-99.
- [20] Peuranen S, Tiihonen K, Apajalahti J, Kettunen A, Saarinen M, Rautonen N. Combination of Polydextrose and Lactitol Affects Microbial Ecosystem and Immune Responses in Rat Gastrointestinal Tract. *British Journal of Nutrition* 2004;91 (6) 905-914.
- [21] Witaicenis A, Fruet AC, Salem L, Di Stasi LC. Dietary Polydextrose Prevents Inflammatory Bowel Disease in Trinitrobenzenesulfonic Acid Model of Rat Colitis. *Journal of Medicinal Food* 2010;13 (6) 1391-1396.
- [22] Legette LL, Lee W, Martin BR, Story JA, Campbell JK, Weaver CM. Prebiotics Enhance Magnesium Absorption and Inulin-Based Fibers Exert Chronic Effects on Calcium Utilization in a Postmenopausal Rodent Model. *J Food Sci* 2012;77 (4) H88-94.
- [23] dos Santos EF, Tsuboi KH, Araújo MR, Ouwehand AC, Andreollo NA, Miyasaka CK. Dietary Polydextrose Increases Calcium Absorption in Normal Rats. *ABCD. Arquivos Brasileiros de Cirurgia Digestiva (São Paulo)* 2009;22 201-205.

- [24] Mineo H, Hara H, Kikuchi H, Sakurai H, Tomita F. Various Indigestible Saccharides Enhance Net Calcium Transport from the Epithelium of the Small and Large Intestine of Rats in Vitro. *Journal of Nutrition* 2001;131 (12) 3243-3246.
- [25] Weaver CM, Martin BR, Story JA, Hutchinson I, Sanders L. Novel Fibers Increase Bone Calcium Content and Strength Beyond Efficiency of Large Intestine Fermentation. *Journal of Agricultural and Food Chemistry* 2010;58 (16) 8952-8957.
- [26] dos Santos EF, Tsuboi KH, Araújo MR, Falconi MA, Ouwehand AC, Andreollo NA, Miyasaka CK. Ingestion of Polydextrose Increase the Iron Absorption in Rats Submitted to Partial Gastrectomy. *Acta Cirurgica Brasileira* 2010;25 518-524.
- [27] Dikeman CL, Fahey Jr GC. Viscosity as Related to Dietary Fiber: A Review. *Critical Reviews in Food Science and Nutrition* 2006;46 (8) 649-663.
- [28] Kapur NK, Ashen D, Blumenthal RS. High Density Lipoprotein Cholesterol: An Evolving Target of Therapy in the Management of Cardiovascular Disease. *Vascular Health and Risk Management* 2008;4 (1) 39-57.
- [29] Brown L, Rosner B, Willett WW, Sacks FM. Cholesterol-Lowering Effects of Dietary Fiber: A Meta-Analysis. *American Journal of Clinical Nutrition* 1999;69 (1) 30-42.
- [30] Hunninghake DB, Miller VT, LaRosa JC, Kinosian B, Jacobson T, Brown V, Howard WJ, Edelman DA, O'Connor RR. Long-Term Treatment of Hypercholesterolemia with Dietary Fiber. *American Journal of Medicine* 1994;97 (6) 504-508.
- [31] Jenkins DJA, Kendall CWC, Vuksan V, Augustin LSA, Mehling C, Parker T, Vidgen E, Lee B, Faulkner D, Seyler H, Josse R, Leiter LA, Connelly PW, Fulgoni Iii V. Effect of Wheat Bran on Serum Lipids: Influence of Particle Size and Wheat Protein. *Journal of the American College of Nutrition* 1999;18 (2) 159-165.
- [32] Jenkins DJA, Vuksan V, Kendall CWC, Würsch P, Jeffcoat R, Waring S, Mehling CC, Vidgen E, Augustin LSA, Wong E. Physiological Effects of Resistant Starches on Fecal Bulk, Short Chain Fatty Acids, Blood Lipids and Glycemic Index. *Journal of the American College of Nutrition* 1998;17 (6) 609-616.
- [33] Truswell AS. Dietary Fibre and Plasma Lipids. *European Journal of Clinical Nutrition* 1995;49 (SUPPL. 3) S105-S109.
- [34] Jenkins DJA, Kendall CWC, Axelsen M, Augustin LSA, Vuksan V. Viscous and Nonviscous Fibres, Nonabsorbable and Low Glycaemic Index Carbohydrates, Blood Lipids and Coronary Heart Disease. *Current Opinion in Lipidology* 2000;11 (1) 49-56.
- [35] Ellegård L, Andersson H. Oat Bran Rapidly Increases Bile Acid Excretion and Bile Acid Synthesis: An Ileostomy Study. *European Journal of Clinical Nutrition* 2007;61 (8) 938-945.
- [36] Marlett JA, Fischer MH. A Poorly Fermented Gel from Psyllium Seed Husk Increases Excreta Moisture and Bile Acid Excretion in Rats. *Journal of Nutrition* 2002;132 (9) 2638-2643.
- [37] Gunness P, Flanagan BM, Gidley MJ. Molecular Interactions between Cereal Soluble Dietary Fibre Polymers and a Model Bile Salt Deduced from ¹³C Nmr Titration. *Journal of Cereal Science* 2010;52 (3) 444-449.

- [38] Shelat KJ, Vilaplana F, Nicholson TM, Gidley MJ, Gilbert RG. Diffusion and Rheology Characteristics of Barley Mixed Linkage B-Glucan and Possible Implications for Digestion. *Carbohydrate Polymers* 2011;86 (4) 1732-1738.
- [39] Potter JG, Coffman KP, Reid RL. Effect of Test Meals of Varying Dietary Fiber Content on Plasma Insulin and Glucose Response. *American Journal of Clinical Nutrition* 1981;34 (3) 328-334.
- [40] Burton-Freeman B. Dietary Fiber and Energy Regulation. *Journal of Nutrition* 2000;130 (2 SUPPL.) 272S-275S.
- [41] Wolever TMS, Spadafora PJ, Cunnane SC, Pencharz PB. Propionate Inhibits Incorporation of Colonic [1,2-¹³C]Acetate into Plasma Lipids in Humans. *American Journal of Clinical Nutrition* 1995;61 (6) 1241-1247.
- [42] Choi YS, Cho SH, Kim HJ, Lee HJ. Effects of Soluble Dietary Fibers on Lipid Metabolism and Activities of Intestinal Disaccharidases in Rats. *Journal of Nutritional Science and Vitaminology* 1998;44 (5) 591-600.
- [43] Oku T, Fujii Y, Okamatsu H. Polydextrose as Dietary Fiber - Hydrolysis by Digestive Enzyme and Its Effect on Gastrointestinal Transit-Time in Rats. *Journal of Clinical Biochemistry and Nutrition* 1991;11 (1) 31-40.
- [44] Choe M, Kim JD, Ju JS. Effects of Polydextrose and Hydrolysed Guar Gum on Lipid Metabolism of Normal Rats with Different Levels of Dietary Fat. *Korean Journal of Nutrition* 1992;25 (3) 211-220.
- [45] Pronczuk A, Hayes KC. Hypocholesterolemic Effect of Dietary Polydextrose in Gerbils and Humans. *Nutrition Research* 2006;26 (1) 27-31.
- [46] Shimomura Y, Maeda K, Nagasaki M, Matsuo Y, Murakami T, Bajotto G, Sato J, Selno T, Kamiwaki T, Suzuki M. Attenuated Response of the Serum Triglyceride Concentration to Ingestion of a Chocolate Containing Polydextrose and Lactitol in Place of Sugar. *Bioscience Biotechnology and Biochemistry* 2005;69 (10) 1819-1823.
- [47] Saku K, Yoshinaga K, Okura Y, Ying H, Harada R, Arakawa K. Effects of Polydextrose on Serum-Lipids, Lipoproteins, and Apolipoproteins in Health Subjects. *Clinical Therapeutics* 1991;13 (2) 254-258.
- [48] Liu S, Tsai CE. Effects of Biotechnically Synthesized Oligosaccharides and Polydextrose on Serum Lipids in the Human. *Journal of the Chinese Nutrition Society* 1995;20 (1) 1-12.
- [49] Jie Z, Bang-Yao L, Ming-Jie X, Hai-Wei L, Zu-Kang Z, Ting-Song W, Craig SA. Studies on the Effects of Polydextrose Intake on Physiologic Functions in Chinese People. *American Journal of Clinical Nutrition* 2000;72 (6) 1503-1509.
- [50] Riccardi G, Rivellese A, Pacioni D. Separate Influence of Dietary Carbohydrate and Fibre on the Metabolic Control in Diabetes. *Diabetologia* 1984;26 (2) 116-121.
- [51] Rivellese A, Riccardi G, Giacco A. Effect of Dietary Fibre on Glucose Control and Serum Lipoproteins in Diabetic Patients. *Lancet* 1980;2 (8192) 447-449.
- [52] Schwab U, Louheranta A, Torronen A, Uusitupa M. Impact of Sugar Beet Pectin and Polydextrose on Fasting and Postprandial Glycemia and Fasting Concentrations of Serum Total and Lipoprotein Lipids in Middle-Aged Subjects with Abnormal Glucose Metabolism. *European Journal of Clinical Nutrition* 2006;60 (9) 1073-1080.

- [53] Cicek B, Arslan P, Kelestimur F. The Effects of Oligofructose and Polydextrose on Metabolic Control Parameters in Type-2 Diabetes. *Pakistan Journal of Medical Sciences* 2009;25 (4) 573-578.
- [54] Chinevere TD, Sawyer RD, Creer AR, Conlee RK, Parcell AC. Effects of L-Tyrosine and Carbohydrate Ingestion on Endurance Exercise Performance. *Journal of Applied Physiology* 2002;93 (5) 1590-1597.
- [55] Vasankari TJ, Ahotupa M. Supplementation of Polydextrose Reduced a Hamburger Meal Induced Postprandial Hypertriglyceridemia. *Circulation* 2005;112 (17) 3849.
- [56] Movva R, Rader DJ. Laboratory Assessment of Hdl Heterogeneity and Function. *Clinical Chemistry* 2008;54 (5) 788-800.
- [57] Kwiterovich PO, Jr. Lipoprotein Heterogeneity: Diagnostic and Therapeutic Implications. *American Journal of Cardiology* 2002;90 (8, Supplement 1) 1-10.
- [58] Salonen JT, Salonen R, Seppanen K, Rauramaa R, Tuomilehto J. Hdl, Hdl2, and Hdl3 Subfractions, and the Risk of Acute Myocardial Infarction. A Prospective Population Study in Eastern Finnish Men. *Circulation* 1991;84 (1) 129-139.
- [59] Lamarche B, Moorjani S, Cantin B, Dagenais GR, Lupien PJ, Despres JP. Associations of Hdl2 and Hdl3 Subfractions with Ischemic Heart Disease in Men. Prospective Results from the Quebec Cardiovascular Study. *Arteriosclerosis, Thrombosis, and Vascular Biology* 1997;17 (6) 1098-1105.
- [60] Stampfer MJ, Sacks FM, Salvini S, Willett WC, Hennekens CH. A Prospective Study of Cholesterol, Apolipoproteins, and the Risk of Myocardial Infarction. *The New England Journal of Medicine* 1991;325 (6) 373-381.
- [61] Yu S, Yarnell JW, Sweetnam P, Bolton CH. High Density Lipoprotein Subfractions and the Risk of Coronary Heart Disease: 9-Years Follow-up in the Caerphilly Study. *Atherosclerosis* 2003;166 (2) 331-338.
- [62] Morgan J, Carey C, Lincoff A, Capuzzi D. High-Density Lipoprotein Subfractions and Risk of Coronary Artery Disease. *Current Atherosclerosis Reports* 2004;6 (5) 359-365.
- [63] Bosello O, Cominacini L, Zocca I, Garbin U, Ferrari F, Davoli A. Effects of Guar Gum on Plasma Lipoproteins and Apolipoproteins C-Ii and C-Iii in Patients Affected by Familial Combined Hyperlipoproteinemia. *The American Journal of Clinical Nutrition* 1984;40 (6) 1165-1174.
- [64] McIvor ME, Cummings CC, Van Duyn MA, Leo TA, Margolis S, Behall KM, Michnowski JE, Mendeloff AI. Long-Term Effects of Guar Gum on Blood Lipids. *Atherosclerosis* 1986;60 (1) 7-13.
- [65] Anderson JW, O'Neal DS, Riddell-Mason S, Floore TL, Dillon DW, Oeltgen PR. Postprandial Serum Glucose, Insulin, and Lipoprotein Responses to High- and Low-Fiber Diets. *Metabolism: Clinical and Experimental* 1995;44 (7) 848-854.
- [66] Behall KM, Scholfield DJ, Hallfrisch J. Effect of Beta-Glucan Level in Oat Fiber Extracts on Blood Lipids in Men and Women. *Journal of the American College of Nutrition* 1997;16 (1) 46-51.
- [67] Williams PT, Krauss RM, Vranizan KM, Stefanick ML, Wood PDS, Lindgren FT. Associations of Lipoproteins and Apolipoproteins with Gradient Gel Electrophoresis

- Estimates of High Density Lipoprotein Subfractions in Men and Women. *Arteriosclerosis and Thrombosis* 1992;12 (3) 332-340.
- [68] Krauss RM. Lipoprotein Subfractions and Cardiovascular Disease Risk. *Current Opinion in Lipidology* 2010;21 (4) 305-311.
- [69] Ozawa H, Kobayashi T, Sakane H, Imafuku S, Mikami Y, Homma Y. Effects of Dietary Fiber Polydextrose Feeding on Plasma Lipids Levels and Diurnal Change in Plasma Sugar, Insulin, and Blood Pressure Levels. *Nippon Eiyo Shokuryo Gakkaishi* 1993;46 (5) 395-399.
- [70] Lefebvre P, Cariou B, Lien F, Kuipers F, Staels B. Role of Bile Acids and Bile Acid Receptors in Metabolic Regulation. *Physiological Reviews* 2009;89 (1) 147-191.
- [71] Wang DQ. Regulation of Intestinal Cholesterol Absorption. *Annual Review of Physiology* 2007;69 221-248.
- [72] Ridlon JM, Kang DJ, Hylemon PB. Bile Salt Biotransformations by Human Intestinal Bacteria. *Journal of Lipid Research* 2006;47 (2) 241-259.
- [73] Chiang JYL. Bile Acids: Regulation of Synthesis. *Journal of Lipid Research* 2009;50 (10) 1955-1966.
- [74] Charlton-Menys V, Durrington PN. Human Cholesterol Metabolism and Therapeutic Molecules. *Experimental Physiology* 2008;93 (1) 27-42.
- [75] Lia A, Hallmans G, Sandberg AS, Sundberg B, Aman P, Andersson H. Oat B-Glucan Increases Bile Acid Excretion and a Fiber-Rich Barley Fraction Increases Cholesterol Excretion in Ileostomy Subjects. *American Journal of Clinical Nutrition* 1995;62 (6) 1245-1251.
- [76] Theuvsen E, Mensink RP. Water-Soluble Dietary Fibers and Cardiovascular Disease. *Physiology and Behavior* 2008;94 (2) 285-292.
- [77] Hengst C, Ptok S, Roessler A, Fechner A, Jahreis G. Effects of Polydextrose Supplementation on Different Faecal Parameters in Healthy Volunteers. *International Journal of Food Sciences and Nutrition* 2008;60 (5) 96-105.
- [78] Zacherl C, Eisner P, Engel K-H. In Vitro Model to Correlate Viscosity and Bile Acid-Binding Capacity of Digested Water-Soluble and Insoluble Dietary Fibres. *Food Chemistry* 2011;126 (2) 423-428.
- [79] Murphy O. Non-Polyol Low-Digestible Carbohydrates: Food Applications and Functional Benefits. *British Journal of Nutrition* 2001;85 (Suppl 1) S47-S53.
- [80] Satoh H, Hara T, Murakawa D, Matsuura M, Takata K. Soluble Dietary Fiber Protects against Nonsteroidal Anti-Inflammatory Drug-Induced Damage to the Small Intestine in Cats. *Digestive Diseases and Sciences* 2010;55 (5) 1264-1271.
- [81] Ogata S, Fujimoto K, Iwakiri R, Matsunaga C, Ogawa Y, Koyama T, Sakai T. Effect of Polydextrose on Absorption of Triglyceride and Cholesterol in Mesenteric Lymph-Fistula Rats. *Proceedings of the Society for Experimental Biology and Medicine* 1997;215 (1) 53-58.
- [82] Watanabe K, Iwata K, Tandai Y, Nishizawa M, Yamagishi T, Yoshizawa I. Effects of Soluble Sodium Alginates on the Excretion of Cholesterol, Trp-P-1 and Aflatoxin B 1 in Rats. *Japanese Journal of Toxicology and Environmental Health* 1992;38 (3) 258-262.

- [83] MacDonald IA, Bokkenheuser VD, Winter J. Degradation of Steroids in the Human Gut. *Journal of Lipid Research* 1983;24 (6) 675-700.
- [84] Litvak DA, Hwang KO, Evers BM, Townsend CM, Jr. Induction of Apoptosis in Human Gastric Cancer by Sodium Butyrate. *Anticancer Research* 2000;20 (2A) 779-784.
- [85] Mariadason JM, Corner GA, Augenlicht LH. Genetic Reprogramming in Pathways of Colonic Cell Maturation Induced by Short Chain Fatty Acids: Comparison with Trichostatin a, Sulindac, and Curcumin and Implications for Chemoprevention of Colon Cancer. *Cancer Research* 2000;60 (16) 4561-4572.
- [86] Wong JM, de SR, Kendall CW, Emam A, Jenkins DJ. Colonic Health: Fermentation and Short Chain Fatty Acids. *Journal of Clinical Gastroenterology* 2006;40 (3) 235-243.
- [87] Alvaro A, Solà R, Rosales R, Ribalta J, Anguera A, Masana L, Vallvé JC. Gene Expression Analysis of a Human Enterocyte Cell Line Reveals Downregulation of Cholesterol Biosynthesis in Response to Short-Chain Fatty Acids. *IUBMB Life* 2008;60 (11) 757-764.
- [88] Lin Y, Vonk RJ, Slooff JH, Kuipers F, Smit MJ. Differences in Propionate-Induced Inhibition of Cholesterol and Triacylglycerol Synthesis between Human and Rat Hepatocytes in Primary Culture. *British Journal of Nutrition* 1995;74 (2) 197-207.
- [89] Layden BT, Yalamanchi SK, Wolever TMS, Dunaif A, Lowe Jr WL. Negative Association of Acetate with Visceral Adipose Tissue and Insulin Levels. *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy* 2012;5 49-55.
- [90] Boila RJ, Salomons MO, Milligan LP, Aherne FX. The Effect of Dietary Propionic Acid on Cholesterol Synthesis in Swine. *Nutrition Reports International* 1981;23 (6) 1113-1121.
- [91] Nishina PM, Freedland RA. Effects of Propionate on Lipid Biosynthesis in Isolated Rat Hepatocytes. *Journal of Nutrition* 1990;120 (7) 668-673.
- [92] Wright RS, Anderson JW, Bridges SR. Propionate Inhibits Hepatocyte Lipid Synthesis. *Proceedings of the Society for Experimental Biology and Medicine* 1990;195 (1) 26-29.
- [93] Illman RJ, Topping DL, McIntosh GH, Trimble RP, Storer GB, Taylor MN, Cheng BQ. Hypocholesterolaemic Effects of Dietary Propionate: Studies in Whole Animals and Perfused Rat Liver. *Annals of Nutrition and Metabolism* 1988;32 (2) 97-107.
- [94] Adam A, Levrat-Verny MA, Lopez HW, Leuillet M, Demigné C, Rémésy C. Whole Wheat and Triticale Flours with Differing Viscosities Stimulate Cecal Fermentations and Lower Plasma and Hepatic Lipids in Rats. *Journal of Nutrition* 2001;131 (6) 1770-1776.
- [95] Venter CS, Vorster HH, Cummings JH. Effects of Dietary Propionate on Carbohydrate and Lipid Metabolism in Healthy Volunteers. *American Journal of Gastroenterology* 1990;85 (5) 549-553.
- [96] Beaulieu KE, McBurney MI. Changes in Pig Serum Lipids, Nutrient Digestibility and Sterol Excretion During Cecal Infusion of Propionate. *Journal of Nutrition* 1992;122 (2) 241-245.
- [97] Wolever TMS, Spadafora P, Eshuis H. Interaction between Colonic Acetate and Propionate in Humans. *American Journal of Clinical Nutrition* 1991;53 (3) 681-687.

- [98] Todesco T, Rao AV, Bosello O, Jenkins DJA. Propionate Lowers Blood Glucose and Alters Lipid Metabolism in Healthy Subjects. *American Journal of Clinical Nutrition* 1991;54 (5) 860-865.
- [99] Vogt JA, Wolever TMS. Fecal Acetate Is Inversely Related to Acetate Absorption from the Human Rectum and Distal Colon. *Journal of Nutrition* 2003;133 (10) 3145-3148.
- [100] Mäki vuokko H, Kettunen H, Saarinen M, Kamiwaki T, Yokoyama Y, Stowell J, Rautonen N. The Effect of Cocoa and Polydextrose on Bacterial Fermentation in Gastrointestinal Tract Simulations. *Bioscience Biotechnology and Biochemistry* 2007;71 (8) 1834-1843.
- [101] Makelainen HS, Mäki vuokko HA, Salminen SJ, Rautonen NE, Ouwehand AC. The Effects of Polydextrose and Xylitol on Microbial Community and Activity in a 4-Stage Colon Simulator. *Journal of Food Science* 2007;72 (5) M153-M159.
- [102] Hernot DC, Boileau TW, Bauer LL, Middelbos IS, Murphy MR, Swanson KS, Fahey GC. In Vitro Fermentation Profiles, Gas Production Rates, and Microbiota Modulation as Affected by Certain Fructans, Galactooligosaccharides, and Polydextrose. *Journal of Agricultural and Food Chemistry* 2009;57 (4) 1354-1361.
- [103] Beloshapka AN, Wolff AK, Swanson KS. Effects of Feeding Polydextrose on Faecal Characteristics, Microbiota and Fermentative End Products in Healthy Adult Dogs. *British Journal of Nutrition* 2011;1-7.
- [104] Stowell JD. Prebiotic Potential of Polydextrose. In: Charalampopoulos D, Rastall RA (ed.) *Prebiotics and Probiotics Science and Technology*, Reading: Springer; 2009. p337-352.
- [105] Wang X, Gibson GR. Effects of the in-Vitro Fermentation of Oligofructose and Inulin by Bacteria Growing in the Human Large-Intestine. *Journal of Applied Bacteriology* 1993;75 (4) 373-380.
- [106] Vester Boler BM, Hernot DC, Boileau TW, Bauer LL, Middelbos IS, Murphy MR, Swanson KS, Fahey GC, Jr. Carbohydrates Blended with Polydextrose Lower Gas Production and Short-Chain Fatty Acid Production in an in Vitro System. *Nutrition Research* 2009;29 (9) 631-639.
- [107] Vester Boler BM, Rossoni Sero MC, Bauer LL, Staeger MA, Boileau TW, Swanson KS, Fahey GC. Digestive Physiological Outcomes Related to Polydextrose and Soluble Maize Fibre Consumption by Healthy Adult Men. *British Journal of Nutrition* 2011;106 (12) 1864-1871.
- [108] Mäki vuokko H, Nurmi J, Nurminen P, Stowell J, Rautonen N. In Vitro Effects on Polydextrose by Colonic Bacteria and Caco-2 Cell Cyclooxygenase Gene Expression. *Nutrition and Cancer-An International Journal* 2005;52 (1) 94-104.
- [109] Mäkeläinen H, Ottman N, Forssten S, Saarinen M, Rautonen N, Ouwehand AC. Synbiotic Effects of Galacto-Oligosaccharide, Polydextrose and *Bifidobacterium Lactis* Bi-07 in Vitro. *International Journal of Probiotics and Prebiotics* 2010;5 (4) 203-210.
- [110] Bäckhed F, Ding H, Wang T, Hooper LV, Gou YK, Nagy A, Semenkovich CF, Gordon JI. The Gut Microbiota as an Environmental Factor That Regulates Fat Storage. *Proceedings of the National Academy of Sciences of the United States of America* 2004;101 (44) 15718-15723.

- [111] Martínez I, Wallace G, Zhang C, Legge R, Benson AK, Carr TP, Moriyama EN, Walter J. Diet-Induced Metabolic Improvements in a Hamster Model of Hypercholesterolemia Are Strongly Linked to Alterations of the Gut Microbiota. *Applied and Environmental Microbiology* 2009;75 (12) 4175-4184.
- [112] Cheng S, Munukka E, Wiklund P, Pekkala S, Völgyi E, Xu L, Lyytikäinen A, Marjomäki V, Alen M, Vaahrovuo J, Keinänen-Kiukaanniemi S. Women with and without Metabolic Disorder Differ in Their Gut Microbiota Composition. *Obesity* 2012;20 (5) 1082-1087.
- [113] Patrone V, Ferrari S, Lizier M, Lucchini F, Minuti A, Tondelli B, Trevisi E, Rossi F, Callegari ML. Short-Term Modifications in the Distal Gut Microbiota of Weaning Mice Induced by a High-Fat Diet. *Microbiology* 2012;158 (4) 983-992.
- [114] Hooda S, Boler Vester BM, Serao Rossoni MC, Brulc JM, Staeger MA, Boileau TW, Dowd SE, Fahey GC, Jr., Swanson KS. 454 Pyrosequencing Reveals a Shift in Fecal Microbiota of Healthy Adult Men Consuming Polydextrose or Soluble Corn Fiber. *Journal of Nutrition* 2012;
- [115] Probert HM, Apajalahti JHA, Rautonen N, Stowell J, Gibson GR. Polydextrose, Lactitol, and Fructo-Oligosaccharide Fermentation by Colonic Bacteria in a Three-Stage Continuous Culture System. *Applied and Environmental Microbiology* 2004;70 (8) 4505-4511.
- [116] Truswell AS. Cereal Grains and Coronary Heart Disease. *European Journal of Clinical Nutrition* 2002;56 (1) 1-14.
- [117] Salas-Salvadó J, Bulló M, Pérez-Heras A, Ros E. Dietary Fibre, Nuts and Cardiovascular Diseases. *British Journal of Nutrition* 2006;96 Suppl 2 S46-51.
- [118] Lairon D, Play B, Jourdeuil-Rahmani D. Digestible and Indigestible Carbohydrates: Interactions with Postprandial Lipid Metabolism. *Journal of Nutritional Biochemistry* 2007;18 (4) 217-227.
- [119] Ford ES, Liu S. Glycemic Index and Serum High-Density Lipoprotein Cholesterol Concentration among Us Adults. *Archives of Internal Medicine* 2001;161 (4) 572-576.
- [120] Liu S, Manson JE, Stampfer MJ, Holmes MD, Hu FB, Hankinson SE, Willett WC. Dietary Glycemic Load Assessed by Food-Frequency Questionnaire in Relation to Plasma High-Density-Lipoprotein Cholesterol and Fasting Plasma Triacylglycerols in Postmenopausal Women. *American Journal of Clinical Nutrition* 2001;73 (3) 560-566.
- [121] Ravid Z, Bendayan M, Delvin E, Sane AT, Elchebly M, Lafond J, Lambert M, Mailhot G, Levy E. Modulation of Intestinal Cholesterol Absorption by High Glucose Levels: Impact on Cholesterol Transporters, Regulatory Enzymes, and Transcription Factors. *American Journal of Physiology - Gastrointestinal and Liver Physiology* 2008;295 (5) G873-G885.
- [122] Silbernagel G, Lütjohann D, MacHann J, Meichsner S, Kantartzis K, Schick F, Häring HU, Stefan N, Fritsche A. Cholesterol Synthesis Is Associated with Hepatic Lipid Content and Dependent on Fructose/Glucose Intake in Healthy Humans. *Experimental Diabetes Research* 2012;2012
- [123] Foster-Powell K, Holt SH, Brand-Miller JC. International Table of Glycemic Index and Glycemic Load Values: 2002. *American Journal of Clinical Nutrition* 2002;76 (1) 5-56.

- [124] Shimomura Y, Nagasaki M, Matsuo Y, Maeda K, Murakami T, Sato J, Sato Y. Effects of Polydextrose on the Levels of Plasma Glucose and Serum Insulin Concentrations in Human Glucose Tolerance Test. *Journal of Japanese Association for Dietary Fiber Research* 2004;8 (2) 105-109.
- [125] Tappy L, Le KA. Metabolic Effects of Fructose and the Worldwide Increase in Obesity. *Physiological Reviews* 2010;90 (1) 23-46.
- [126] Knapp BK, Parsons CM, Swanson KS, Fahey GC. Physiological Responses to Novel Carbohydrates as Assessed Using Canine and Avian Models. *Journal of Agricultural and Food Chemistry* 2008;56 (17) 7999-8006.
- [127] Wilson T, Luebke JL, Morcomb EF, Carrell EJ, Leveranz MC, Kobs L, Schmidt TP, Limburg PJ, Vorsa N, Singh AP. Glycemic Responses to Sweetened Dried and Raw Cranberries in Humans with Type 2 Diabetes. *Journal of Food Science* 2010;75 (8) H218-223.
- [128] Kurotobi T, Fukuhara K, Inage H, Kimura S. Glycemic Index and Postprandial Blood Glucose Response to Japanese Strawberry Jam in Normal Adults. *Journal of Nutritional Science and Vitaminology* 2010;56 (3) 198-202.
- [129] Kovacs EMR, Westerterp-Plantenga MS, Saris WHM, Melanson KJ, Goossens I, Geurten P, Brouns F. The Effect of Guar Gum Addition to a Semisolid Meal on Appetite Related to Blood Glucose, in Dieting Men. *European Journal of Clinical Nutrition* 2002;56 (8) 771-778.
- [130] King NA, Craig SAS, Pepper T, Blundell JE. Evaluation of the Independent and Combined Effects of Xylitol and Polydextrose Consumed as a Snack on Hunger and Energy Intake over 10 D. *British Journal of Nutrition* 2005;93 (6) 911-915.
- [131] Monsivais P, Carter BE, Christiansen M, Perrigue MM, Drewnowski A. Soluble Fiber Dextrin Enhances the Satiating Power of Beverages. *Appetite* 2011;56 (1) 9-14.
- [132] Willis HJ, Eldridge AL, Beiseigel J, Thomas W, Slavin JL. Greater Satiety Response with Resistant Starch and Corn Bran in Human Subjects. *Nutrition Research* 2009;29 (2) 100-105.
- [133] Ranawana V, Muller A, Henry JK. Polydextrose: Its Effects on Short-Term Food Intake and Subjective Feelings of Satiety: A Randomized Controlled Study. *European Journal of Nutrition* 2012;
- [134] Saarinen M, Olli K, Hull S, Re R, Stowell J, Tiihonen K. The Effects of Polydextrose on Satiety in Humans. In 2nd Swiss Food Tech Day 2011, "Micronutrients & Functional Ingredients", 11th May 2011. Sisseln, Switzerland.
- [135] Hull S, Re R, Tiihonen K, Viscione L, Wickham M. Consuming Polydextrose in a Mid-Morning Snack Increases Acute Satiety Measurements and Reduces Subsequent Energy Intake at Lunch in Healthy Human Subjects. 2012 Manuscript in Preparation.
- [136] Lin HV, Frassetto A, Kowalik EJ, Jr., Nawrocki AR, Lu MM, Kosinski JR, Hubert JA, Szeto D, Yao X, Forrest G, Marsh DJ. Butyrate and Propionate Protect against Diet-Induced Obesity and Regulate Gut Hormones Via Free Fatty Acid Receptor 3-Independent Mechanisms. *PLoS One* 2012;7 (4) e35240.
- [137] Leuvenink HGD, Bleumer EJB, Bongers LJGM, Van Bruchem J, Van Der Heide D. Effect of Short-Term Propionate Infusion on Feed Intake and Blood Parameters in

- Sheep. *American Journal of Physiology - Endocrinology and Metabolism* 1997;272 (6 35-6) E997-E1001.
- [138] Oba M, Allen MS. Intraruminal Infusion of Propionate Alters Feeding Behavior and Decreases Energy Intake of Lactating Dairy Cows. *Journal of Nutrition* 2003;133 (4) 1094-1099.
- [139] Karaki SI, Tazoe H, Hayashi H, Kashiwabara H, Tooyama K, Suzuki Y, Kuwahara A. Expression of the Short-Chain Fatty Acid Receptor, Gpr43, in the Human Colon. *Journal of Molecular Histology* 2008;39 (2) 135-142.
- [140] Tolhurst G, Heffron H, Lam YS, Parker HE, Habib AM, Diakogiannaki E, Cameron J, Grosse J, Reimann F, Gribble FM. Short-Chain Fatty Acids Stimulate Glucagon-Like Peptide-1 Secretion Via the G-Protein-Coupled Receptor Ffar2. *Diabetes* 2012;61 (2) 364-371.
- [141] Vanhoutvin SA, Troost FJ, Hamer HM, Lindsey PJ, Koek GH, Jonkers DM, Kodde A, Venema K, Brummer RJ. Butyrate-Induced Transcriptional Changes in Human Colonic Mucosa. *PLoS ONE* 2009;4 (8) e6759.
- [142] Bassaganya-Riera J, DiGuardo M, Viladomiu M, de Horna A, Sanchez S, Einerhand AWC, Sanders L, Hontecillas R. Soluble Fibers and Resistant Starch Ameliorate Disease Activity in Interleukin-10-Deficient Mice with Inflammatory Bowel Disease. *Journal of Nutrition* 2011;141 (7) 1318-1325.
- [143] Wachtershauser A, Loitsch SM, Stein J. Ppar-Gamma Is Selectively Upregulated in Caco-2 Cells by Butyrate. *Biochemical and Biophysical Research Communications* 2000;272 (2) 380-385.
- [144] Putaala H, Makivuokko H, Tiihonen K, Rautonen N. Simulated Colon Fiber Metabolome Regulates Genes Involved in Cell Cycle, Apoptosis, and Energy Metabolism in Human Colon Cancer Cells. *Molecular and Cellular Biochemistry* 2011;357 (1-2) 235-245.
- [145] Bunger M, van den Bosch HM, van der Meijde J, Kersten S, Hooiveld GJEJ, Muller M. Genome-Wide Analysis of Ppar{Alpha} Activation in Murine Small Intestine. *Physiological Genomics* 2007;15 (4) 837-845.
- [146] de Vogel-van den Bosch HM, Bunger M, de Groot PJ, Bosch-Vermeulen H, Hooiveld GJ, Muller M. Pparalpha-Mediated Effects of Dietary Lipids on Intestinal Barrier Gene Expression. *BMC Genomics* 2008;9 231.
- [147] Ranhotra HS. Long-Term Caloric Restriction up-Regulates Ppar Gamma Co-Activator 1 Alpha (Pgc-1 α) Expression in Mice. *Indian Journal of Biochemistry and Biophysics* 2010;47 (5) 272-277.
- [148] Rera M, Bahadorani S, Cho J, Koehler Christopher L, Ulgherait M, Hur Jae H, Ansari William S, Lo Jr T, Jones DL, Walker David W. Modulation of Longevity and Tissue Homeostasis by the Drosophila Pgc-1 Homolog. *Cell Metabolism* 2011;14 (5) 623-634.
- [149] Finck BN, Gropler MC, Chen Z, Leone TC, Croce MA, Harris TE, Lawrence, Jr., Kelly DP. Lipin 1 Is an Inducible Amplifier of the Hepatic Pgc-1[Alpha]/Ppar[Alpha] Regulatory Pathway. *Cell Metabolism* 2006;4 (3) 199-210.
- [150] Suviolahti E, Reue K, Cantor RM, Phan J, Gentile M, Naukkarinen J, Soro-Paavonen A, Oksanen L, Kaprio J, Rissanen A, Salomaa V, Kontula K, Taskinen MR, Pajukanta P,

- Peltonen L. Cross-Species Analyses Implicate Lipin 1 Involvement in Human Glucose Metabolism. *Human Molecular Genetics* 2006;15 (3) 377-386.
- [151] Yao-Borengasser A, Rasouli N, Varma V, Miles LM, Phanavanh B, Starks TN, Phan J, Spencer Iii HJ, McGehee Jr RE, Reue K, Kern PA. Lipin Expression Is Attenuated in Adipose Tissue of Insulin-Resistant Human Subjects and Increases with Peroxisome Proliferator-Activated Receptor γ Activation. *Diabetes* 2006;55 (10) 2811-2818.
- [152] Kruit JK, Groen AK, van Berkel TJ, Kuipers F. Emerging Roles of the Intestine in Control of Cholesterol Metabolism. *World Journal of Gastroenterology* 2006;12 (40) 6429-6439.
- [153] Field FJ, Watt K, Mathur SN. Origins of Intestinal Abca1-Mediated Hdl-Cholesterol. *Journal of Lipid Research* 2008;49 (12) 2605-2619.
- [154] Brunham LR, Kruit JK, Iqbal J, Fievet C, Timmins JM, Pape TD, Coburn BA, Bissada N, Staels B, Groen AK, Hussain MM, Parks JS, Kuipers F, Hayden MR. Intestinal Abca1 Directly Contributes to Hdl Biogenesis in Vivo. *Journal of Clinical Investigation* 2006;116 (4) 1052-1062.
- [155] Boadu E, Choi HY, Lee DWK, Waddington EI, Chan T, Asztalos B, Vance JE, Chan A, Castro G, Francis GA. Correction of Apolipoprotein a-I-Mediated Lipid Efflux and High Density Lipoprotein Particle Formation in Human Niemann-Pick Type C Disease Fibroblasts. *Journal of Biological Chemistry* 2006;281 (48) 37081-37090.
- [156] De Preter V, Falony G, Windey K, Hamer HM, De Vuyst L, Verbeke K. The Prebiotic, Oligofructose-Enriched Inulin Modulates the Faecal Metabolite Profile: An in Vitro Analysis. *Molecular Nutrition and Food Research* 2010;54 (12) 1791-1801.
- [157] Dullens SPJ, Mensink RP, Mariman ECM, Plat J. Differentiated Caco-2 Cells as an in-Vitro Model to Evaluate De-Novo Apolipoprotein a-L Production in the Small Intestine. *European Journal of Gastroenterology and Hepatology* 2009;21 (6) 642-649.
- [158] Gylling H. Cholesterol Metabolism and Its Implications for Therapeutic Interventions in Patients with Hypercholesterolaemia. *International Journal of Clinical Practice* 2004;58 (9) 859-866.
- [159] Sviridov DD, Safonova IG, Talalaev AG. Regulation of Cholesterol Synthesis in Isolated Epithelial Cells of Human Small Intestine. *Lipids* 1986;21 (12) 759-763.
- [160] Dietschy JM, Siperstein MD. Effect of Cholesterol Feeding and Fasting on Sterol Synthesis in Seventeen Tissues of the Rat. *Journal of Lipid Research* 1967;8 (2) 97-104.
- [161] Dietschy JM, Wilson JD. Regulation of Cholesterol Metabolism. *New England Journal of Medicine* 1970;282 (21) 1179-1183.
- [162] Hara H, Haga S, Aoyama Y, Kiriya S. Short-Chain Fatty Acids Suppress Cholesterol Synthesis in Rat Liver and Intestine. *Journal of Nutrition* 1999;129 (5) 942-948.