Carbohydrate Digestibility and Metabolic Effects\textsuperscript{1,2}

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Abstract

There is a history of interest in the metabolic effects of alterations in small intestinal digestion and colonic fermentation of carbohydrate. It is believed that the rate of digestion of carbohydrate determines the place and form in which carbohydrate is absorbed. Slowly absorbed or lente carbohydrate sources may reduce postprandial glucose surges and the need for insulin with important implications for lowering coronary heart disease risk and reducing diabetes incidence. Carbohydrates that are not digested in the small intestine will enter the colon, and those that are fermentable will be salvaged as short-chain fatty acids in the colon and at the same time may stimulate colonic microflora, such as bifidobacteria. This process may have metabolic effects in the gut and throughout the host, possibly related to short-chain fatty acid products, although these effects are less well documented. One important aspect of colonic fermentation is the stimulation of certain populations of the colonic microflora, which may assist in the biotransformation of bioactive food components including the cleaving of plant phenolics from their glycone to produce the more rapidly absorbed aglycone. However, human studies have been limited. Therefore, further studies are required to explore these important aspects of metabolism related to the rate of carbohydrate absorption and fermentation and their implications in health and disease. J. Nutr. 137: 2539S–2546S, 2007.

Introduction

Delayed or malabsorbed dietary components, specifically carbohydrates, may have significant implications in the pathogenesis and treatment of metabolic disorders. This is of particular importance at a time when the incidence of the metabolic syndrome, obesity, and diabetes continue to rise in Western societies (1). Dietary carbohydrates that are slowly digested and require less insulin for their disposal may benefit those with impaired carbohydrate tolerance. Fermentable carbohydrates that are not digested enter the colon, where they are available for bacterial fermentation and alter the environment by enhancing SCFA production (acetate, propionate, and butyrate). In addition, bioactive substances such as phytoestrogens may be converted to more active forms, and their absorption from the colon may be enhanced (2). Specific SCFA have also been linked to reducing the risk of developing gastrointestinal disorders, cancer, and cardiovascular disease (CVD). As a consequence, attention has been drawn to dietary strategies that promote a change to slowly digested carbohydrates to increase fermentation and thereby reduce the risk of coronary heart disease, diabetes, and cancer.

Carbohydrate digestion

Oligofructose and inulin are not digested in the small intestine. The structure consists of $\beta-(2\rightarrow1)$ fructosyl-fructose linkages with or without a starting $\alpha$-d-glucose moiety (3). Available carbohydrates are $\alpha$-linked sugar units that are initially broken down by salivary and then pancreatic amylase to glucose, maltose, and maltotriose. The maltose and maltotriose, together with sucrose, are further split to component sugars and absorbed through the action of brush border sucrase-isomaltase with lactose split by lactase. Glucose is absorbed by active transport and fructose and galactose by active transport and facilitated diffusion.

Malabsorption of carbohydrates

Traditionally, the amount of carbohydrate available for colonic bacterial fermentation has been determined by the amount of dietary fiber present in foods. However, some of the “available carbohydrate” (i.e., “available” for small intestinal absorption: total carbohydrate minus dietary fiber) in many foods may also escape digestion in the small intestine in appreciable amounts and become available for fermentation by colonic microflora (4). Early studies in ileostomates were conducted to determine carbohydrate losses with different types of foods that vary in...
fiber and available carbohydrate content (5,6). Certain foods have been related to a greater proportionate loss of carbohydrate compared with others: specifically lentils and other legumes, the β-glucan-containing cereals oat bran and barley, and also pumpernickel bread, where the whole grain structure is preserved (Fig. 1) (5,6). Other studies have also shown that available carbohydrate of many starchy foods is incompletely digested and absorbed in the normal small intestine (7,8). A significant positive association was also found between carbohydrate malabsorption and fiber content of the food (Fig. 2) (6,9). This suggests that dietary fiber content of foods tends to determine the amount of available carbohydrate entering the colon. Not unexpectedly, a significant inverse association was observed between glycemic indices of foods, a concept that is discussed later, and losses in the ileal effluent (Fig. 3) (6).

Many factors may influence the digestion of carbohydrates in the small intestine, including the rate of digestion (10,11), the food form (physical form, particle size) (12), type of preparation (cooking method and processing) (12–15), type of starch (amylose or amylopectin) (12,16), presence of antinutrients such as α-amylase inhibitors (17,18), transit time (19), and amount of fiber, fat, and proteins (20,21).

Prebiotics, such as oligofructose and inulin, are an emerging functional food associated with suggested improvements in health. Administration of these dietary components promotes the growth of specific bacteria, especially bifidobacteria (22) and lactobacillus, which have defined metabolic functions (23). Studies involving patients with ileostomies have shown that 88% and 89% of inulin and oligofructose, respectively, are recovered in the effluent (24,25). These oligosaccharides are examples of carbohydrates that are almost entirely not digested in the small intestine, a characteristic that has led to growing research on their effects on colonic and systemic health.

Concept of glycemic index
The classic view that the overall metabolic significance of the rate of carbohydrate digestion (i.e., postprandial blood glucose response) was determined by chain length (i.e., “simple” vs. “complex” carbohydrates) has been questioned. This question-giving gave rise to the concept of the glycemic index (GI), and it was suggested that slowly digested carbohydrates, as an extension of the dietary fiber hypothesis first proposed by Burkitt and Trowell (26), may have metabolic benefits in relation to diabetes and to the reduction of coronary heart disease risk (Table 1) (27). The nature of the carbohydrate source may therefore be important, independent of the fiber content. The GI is a quantitative classification of carbohydrate foods based on the rate of carbohydrate absorption as reflected in the glycemic response (10,37). Research in the area of GI and its clinical application has been greatly facilitated by comprehensive GI food tables (38). Furthermore, the concept of glycemic load (GL) has been developed to assess the total glycemic impact of the diet: it is the product of dietary GI and available dietary carbohydrate (39).

GI and chronic diseases
The rising incidence of metabolic disorders such as diabetes and associated disorders has increased interest in nutrition interventions as a means of tackling this growing problem. As a result, there has been renewed interest in the use of the GI and GL as a nutrition strategy to prevent and manage chronic diseases. However, this renewed interest has also stimulated controversy (12,40).

Epidemiological studies have suggested that low-GI diets may play a role in reducing the risk of CHD, diabetes, and certain cancers. Low-GI diets have been observed to be negatively associated with HDL-C, suggesting that low-GI diets may preserve HDL-C (41,42). In the Women’s Health Study, GI was positively associated with C-reactive protein (43), a marker for systemic inflammation that is associated with an increase in CVD risk (44).

Many studies have explored the effect of low-GI diets on coronary heart disease risk factors. In one study, plasminogen activator inhibitor-1 (PAI-1) levels, a marker of impaired fibrinolysis, was reduced (45), and in another concerning hyperlipidemia, 1 mo on a low-GI diet reduced LDL cholesterol (LDL-C) and triglycerides (TG) in those with higher TG levels, despite no significant difference in body weight (46). A low-GI diet has been compared with a low-fat diet during weight loss, where a low-GI diet showed marked improvements in heart disease risk factors such as insulin resistance, TG, C-reactive protein, and blood pressure while subjects consumed the low-GL diet (47).

In studies that have assessed its effect on the development of CVD directly, low-GI diets appears to have a protective role. The Nurses’ Health Study demonstrated a direct relation between fatal and nonfatal myocardial infarction and GI as well as GL (48). Dietary GI has been suggested to be of greater important in those with insulin resistance because an association was observed with dietary GI and those with body mass index >23 kg/m². On the other hand, no significant association of GI or GL and coronary heart disease was seen in the Zutphen study of older men (49), possibly because of the smaller sample size and demographics, such as age, at the start of study.

Several studies have looked at dietary GI in relation to the development and management of Type 2 diabetes. A recent meta-analysis of low-GI diets compared with conventional or high-GI diets in the management of diabetes found that glycated proteins were reduced 7.4% and HbA1c by 0.43% more on the low-GI diet than on the high-GI diet (50). As observed in the UKPDS, any reduction in HbA1c, no matter how small, improves prognosis. It was observed that a 1% reduction in mean HbA1c resulted in a reduction of 21% in any diabetes-related endpoint, 21% in diabetes-related death, 14% in myocardial infarction, and 37% in microvascular complications (51). Other studies, such as the...
Nurses’ Health Study (52) and the Health Professionals Study (39), found an inverse relationship between GI and risk of developing diabetes. However, this was not observed in the Iowa Women’s Health Study, where the GI and GL were not associated with Type 2 diabetes (53). This study, however, included an elderly cohort, which could introduce a selection bias.

Direct associations between GI and colorectal and breast cancer have been observed in epidemiological studies (54–56). McKeown-Eyssen (57) and Giovannucci (58) were among the first to hypothesize a link between hyperinsulinemia and the development of colorectal cancer and possibly other types of cancer such as breast and prostate (59). This is possibly related to increased insulin-like growth factors in conjunction with a sedentary lifestyle including higher intake of energy and refined carbohydrates and lower intake of fruits and vegetables; however, human data are currently limited. Therefore, low-GI and -GL diets show promise for the prevention and treatment of chronic diseases.

Mechanism of action
It has been hypothesized that the metabolic effect of low-GI foods relates to the rate at which carbohydrates are absorbed from the gut (Fig. 4). Low-GI foods are characterized by the slower rate of carbohydrate absorption (slow-release carbohydrate) resulting in a lower rise in blood glucose levels. Some of the metabolic effects caused by reducing the rate of absorption have been confirmed in studies in healthy men. For example, when a glucose solution was sipped at an even rate over 180 min (sipping) compared with the same amount of glucose taken as a bolus at zero time (28), a marked economy in insulin secretion and lower serum FFA levels were observed with sipping. A similar improvement is also observed with low-GI meals, where a slower rate of glucose absorption reduces the postprandial rise in gut hormones (e.g., incretins) and the demand for insulin. Furthermore, the prolonged absorption of carbohydrate over time will suppress FFA synthesis (28,60) and counterregulatory responses (28,61). Over time, with lower FFA concentrations and sustained tissue insulinization (tissues metabolizing glucose following secretion of insulin), glucose is withdrawn from the circulation at a faster rate. As a result, blood glucose concentrations return toward baseline despite continued glucose absorption from gut. Therefore, a reduction in the rise in peak postprandial and incremental area under the curve for blood glucose are observed. Furthermore, there is a “second meal” effect such that an IV glucose tolerance test shows more rapid uptake of glucose (increased $K_G$) after sipping than after the bolus drink (28).

Carbohydrates, SCFA, and colonic fermentation
Carbohydrates resistant to digestion and those that escape absorption in the small intestine are available for colonic bacterial fermentation resulting in the production of SCFA (acetic, butyric, and propionic acids) together with gases (CO$_2$, CH$_4$, and H$_2$) and heat (62,63). Butyrate has been hypothesized to reduce the risk of colon cancer and to benefit inflammatory bowel disease (64–66). Specifically, increases in SCFA production have been associated with decreased pH$_4$, which may reduce potential pathogenic clostridia, decreased solubility of bile acids, increased absorption of minerals (indirectly), and reduced ammonia absorption by the protonic dissociation of ammonia.

FIGURE 2 Carbohydrate losses for foods in relation to fiber content per 80-g carbohydrate portion [adapted from Jenkins et al. (6)].
and other amines (i.e., the formation of the less diffusible NH$_4^+$ compared with the diffusible NH$_3$) (63,67–70).

The major source of fermentable carbohydrates are the resistant starches. It is estimated that 5–20% of dietary starch is not absorbed in the small intestine (5–7,71,72). Soluble and insoluble fibers are fermented to varying degrees. However, insoluble fibers (e.g., lignans, cellulose, and some hemicelluloses) that are resistant to colonic fermentation may carry with them fermentable carbohydrate substrate, including starches and sugars, although their major role is in fecal bulking. Soluble fibers (e.g., pectins, gums, mucilages, some hemicelluloses, as well as inulin-type fructans) are generally more completely fermented with little effect in increasing fecal bulk. Most fiber-containing foods contain about one-third soluble and two-thirds insoluble fiber (63).

The production of SCFA is determined by a number of factors, including the number and types of microflora present in the colon (67), type of substrate (73), and gut transit time (73–75). In general, fecal SCFA production is in the order acetate > propionate > butyrate (62) in a molar ratio of ~60:20:20, respectively (76). Absorption of SCFA in the cecum and the colon is a very efficient process with only 5–10% being excreted in the feces (67,77–79). Two proposed mechanisms of absorption are 1) diffusion of protonated SCFA and 2) anion exchange (73). Once absorbed, SCFA are metabolized at 3 major sites in the body: 1) cells of cecocolonic epithelium that use butyrate as the major substrate for maintenance-energy-producing pathways; 2) liver cells that metabolize residual butyrate with propionate used for gluconeogenesis and 50–70% of acetate is also taken up by the liver; 3) muscle cells generate energy from the oxidation of residual acetate (67). The primary interest in SCFA has been in relation to colonic function as a result of their uptake and metabolism by colonocytes, specifically butyrate, although SCFA are also metabolic substrates for other tissues of the host.

### SCFA and chronic diseases

CVD. Acetate and propionate have been proposed to have opposing effects in hyperlipidemia, a risk factor for coronary heart disease. Subjects given rectal infusions of acetate and propionate in equivalent ratios showed a dose-dependent increase in serum total cholesterol and TG levels, providing indirect evidence that SCFA are utilized for lipid synthesis (80). In a subsequent study by the same research group, rectal infusions of a mixture of acetate and propionate attenuated the serum cholesterol increase observed when acetate infusion was given alone. However, rectal infusions of propionate alone did not affect lipids or TG in healthy young men and women (81). These results support the idea that propionate inhibits the utilization of acetate for cholesterol synthesis. However, dietary trials have been inconsistent. One-week intakes of 2.7 g of sodium propionate given in bread (82) and 7.5 g sodium propionate taken as a capsule (83) did not affect serum lipids, although one study showed that 5.4 g of propionate given daily for 2 wk lowered LDL-C and total cholesterol in subjects with total cholesterol >5.5 mmol/L (84). Animal studies suggest that propionate inhibits cholesterol synthesis by inhibiting both 3-hydroxyl-3-methylglutaryl-CoA synthase and 3-hydroxy-3-methylglutaryl-CoA reductase (85,86).

Inulin-type fructans are bifidogenic and have been associated with hypolipidemic effects. Although a number of mechanisms have been proposed, increased propionate production, resulting in a decreased acetate:propionate ratio, has been one of the suggested modes of action. Increased production of propionate, through fermentation, may inhibit cholesterol synthesis (85,87–91). This has been supported in studies with hyperlipidemic experimental animals (87,92) but not supported in other animal studies (93–95). The effect of inulin-type fructans on blood lipids in humans have yielded inconsistent results (96) compared with the animal data; this may be related to species differences. Furthermore, few studies have quantified the synthesis of SCFA, specifically acetate and propionate, with use of prebiotics.

The lack of agreement on the relation between increased colonic fermentation and lipid metabolism may be a result of differences in the chemical composition of the substrate source. Studies with resistant starch have been consistent in showing raised fecal butyrate (97–100). Starch fermentation primarily yields acetate and butyrate, whereas fermentation of pectin and xylan yields acetate alone as the main product (101). Recent human studies found that acute ingestion of a nondigestible monosaccharide, l-rhamnose (25 g), increased serum propionate without increasing acetate (102), but longer-term studies have not shown reduced serum lipids (103). Lactulose, a rapidly fermented dietary fiber, has been shown to result in higher serum
short-chain organic acids, including carbohydrates, may improve glucose tolerance through suppression of hepatic lipogenesis (104).

Colon cancer. Butyrate is the preferred fuel of the colonic epithelial cells but also plays a major role in regulation of cell proliferation and differentiation (62,64,67,107). Glucose is readily absorbed into the blood and, therefore, is not a major source of energy for enterocytes (i.e., very little is available to colonocytes). Up to 70–90% of butyrate is metabolized by the colonocytes. As a result, the vast majority of absorbed glucose is passed to the blood. In vitro and in vivo studies have observed that butyrate has an opposing role, resulting in the “butyrate paradox” (108,109). Butyrate stimulated cell proliferation in normal colonocytes (64,107), but it suppressed proliferation of colon adenocarcinoma cells (110). This inconsistency between in vitro and in vivo studies may be related to the timing of butyrate administration, the butyrate source (i.e., different dietary fibers), and interaction with dietary fat (109). Butyrate also stimulates immunogenicity of cancer cells (111). Acetate and propionate have been shown to induce apoptosis in colorectal tumor cell lines, but to a much smaller extent than butyrate (112,113).

Currently, the mechanisms of action of butyrate in relation to colon cancer are not clearly defined. Butyrate has been shown to inhibit cell proliferation by inducing p21WAFI/Cip1 protein and mRNA levels (114–116), which can block the cell cycle at G1. This blockage may allow DNA checkpoint-mediated repair of genomic instability or mutations (108). Through inhibition of histone deacetylase, apoptosis has been shown to be induced by butyrate through hyperacetylation of histones (H3 and H4) (117). As a result, the DNA is in a more open form (118), which would be ideal if DNA damage had occurred and repair enzymes were necessary to approach the damaged DNA. On the other hand, in the presence of a carcinogen, the open form of the DNA may make it more susceptible to mutation (109). Butyrate can also induce differentiation of neoplastic colonocytes in vitro, resulting in a phenotype that is associated with normal mature cells (119). Accumulation of SCFA in the colon leads to a drop in pH, which decreases the solubility of free bile acids and in turn decreases the production of secondary bile acids, which have potential tumor promoter activity (120). This may be related to the inhibition of colonic bacterial enzyme 7α-dehydroxylase, which degrades primary bile acids to secondary bile acids (121). Increased colonic acidification also increases the availability of calcium for binding to free bile acids and fatty acids, rendering them insoluble (122). The effect of inulin-type fructans on the risk of cancer is discussed in other articles of this Supplement.

Inflammatory bowel. SCFA enemas have been tried as a possible treatment for diversion and ulcerative colitis. Roeder demonstrated that colonocytes of individuals with active and quiescent ulcerative colitis have reduced butyrate oxidation compared with controls (123). It has been suggested that bowel inflammation arises as a result of a lack of luminal SCFA (i.e., state of nutritional deficiency) of the colonic epithelium and a block in the uptake or oxidation of SCFA by colonocytes (124, 125). The latter may be related to a reduction in coenzyme A, a requirement for SCFA oxidation (123), from the production of sulfur-containing compounds by colonic microflora. However, this block in uptake and oxidation may be overcome by raising SCFA to higher-than-normal concentrations in the colonic lumen (125).

The resupply of nutrients, either by surgical reanastomosis or SCFA irrigation, may correct this deficiency. Studies of SCFA enemas containing 60 mmol/L of sodium acetate, 30 mmol/L of sodium propionate, and 40 mmol/L of sodium n-butyrate to 5 patients with diversion colitis for a period of 2–6 wk resulted in disappearance of symptoms and the inflammatory changes observed by endoscopic and histological findings (126). However, another study using the same SCFA enema solution in 13 patients with diversion colitis resulted in no endoscopic or histologic changes after 2 wk (127). The treatment of distal ulcerative colitis with SCFA irrigation has produced inconsistent results (128), some studies showing it to be an effective treatment (129–131) and others not (131,132). These inconsistencies may be related to the type of SCFA used (mixture or butyrate alone), SCFA concentrations, frequency of administration, and duration of treatment. Therefore, the use of SCFA irrigations for the treatment of bowel inflammation has been pursued further because the research to date has been inconclusive. The effects of inulin-type fructans on inflammatory bowel disease are dealt with in another article in this series.

At a time where the rising burden of chronic disease has become a major health concern worldwide related to aging populations and changes in diet and lifestyle, delayed or slowly absorbed carbohydrates as part of the nutrition strategy may play a useful role. Further studies are needed to define possible benefits of low-GI diets, including inulin-type fructans as components of low-GI diets, in long-term randomized controlled trials. The data on increased SCFA production and their health benefits are even more limited. Therefore, although there is a requirement for basic mechanistic studies, most importantly, clinical trials must be undertaken to determine the clinical relevance of diet-induced changes in SCFA production.

Literature Cited


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