Metabolic Effects of Dietary Fiber Consumption and Prevention of Diabetes

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Abstract
A high dietary fiber (DF) intake is emphasized in the recommendations of most diabetes and nutritional associations. It is accepted that viscous and gel-forming properties of soluble DF inhibit macronutrient absorption, reduce postprandial glucose response, and beneficially influence certain blood lipids. Colonic fermentation of naturally available high fiber foods can also be mainly attributed to soluble DF, whereas no difference between soluble and insoluble DF consumption on the regulation of body weight has been observed. However, in prospective cohort studies, it is primarily insoluble cereal DF and whole grains, and not soluble DF, that is consistently associated with reduced diabetes risk, suggesting that further, unknown mechanisms are likely to be involved. Recent research indicates that DF consumption contributes to a number of unexpected metabolic effects independent from changes in body weight, which include improvement of insulin sensitivity, modulation of the secretion of certain gut hormones, and effects on various metabolic and inflammatory markers that are associated with the metabolic syndrome. In this review, we briefly summarize novel findings from recent interventions and prospective cohort studies. We discuss concepts and potential mechanisms that might contribute to the further understanding of the involved processes.

Background
Consumption of soluble dietary fiber (DF) reduces postprandial glucose responses after carbohydrate-rich meals, as well as lowering total and LDL cholesterol levels. These effects are likely explained the viscous and/or gel-forming properties of soluble DF, which thereby slow gastric emptying and macronutrient absorption from the gut. However, it is not soluble DF, but mainly the consumption of insoluble cereal DF and whole grains, that is consistently associated with reduced risk of type 2 diabetes in large prospective cohort studies. A number of recent studies give novel insights that might help establish a metabolic link between insoluble DF consumption and reduced diabetes risk. Potential candidates are improved insulin sensitivity and the modulation of inflammatory markers, as well as direct and indirect influences on the gut microbiota (Fig. 1).

Definition and types of DF
DF are highly complex substances that can be described as any nondigestible carbohydrates and lignins not degraded in the upper gut. Commonly, DF are classified according to their solubility in water, even though grading according to viscosity, gel-forming capabilities, or fermentation rate by the gut microbiota might be physiologically more relevant. Most DF is fermented to some degree. However, fermentation rates of DF widely vary, with soluble DF (i.e., pectin, inulin, and β-glucans) and insoluble resistant starch and oligosaccharides tending to be more readily fermented than cereal DF (i.e., cellulose and hemicelluloses). Foods are assumed to be whole grains if all components of the kernel (i.e., bran, germ, and endosperm) are present in their natural proportions. Whole grain food products generally contain some 12% of total (mainly insoluble cereal) DF, and there is a strong correlation between whole grain and cereal DF intake. Some bran derived food products contain up to 25% of DF. Importantly, definition of whole grain both in cohort studies and on labels of commercially available cereal products typically does not require an intact kernel. In U.S. cohorts, whole grain and bran products from corn and wheat are the main sources of cereal DF. Main sources of soluble DF are fruits and vegetables and, to a smaller extent, products from oat and barley that are rich in both insoluble DF and soluble β-glucans. It is, however, important to state that most naturally available high-fiber foods contain both soluble and insoluble fiber in varying amounts.

DF and risk of diabetes in prospective cohort studies
It is commonly assumed that beneficial effects of high fiber diets [fiber intake >25 g/d in women and >38 g/d in men] can mainly be attributed to viscous and/or gel-forming properties of soluble DF. Therefore, analyzing results from prospective cohort studies separately for foods high in “active” soluble DF and “inactive” insoluble DF should be expected to show stronger protective associations for soluble DF. However, this hypothesis is not supported by the available data. A recent meta-analysis that included 328,212 subjects showed no association with reduced diabetes risk both for fruit [relative risk for extreme quintiles (RR) 0.96; 95% CI 0.88–1.04] and vegetable (RR 1.04; 95% CI 0.94–1.15) DF intake. In contrast, a high intake of cereal DF was significantly associated with markedly reduced diabetes risk in most studies (RR 0.67; 95% CI 0.62–0.72). Pooled data for 6 prospective cohort studies including 286,125 subjects indicate that a 2-serving-per-day increment in whole grain consumption might remarkably reduce diabetes risk by 21% (3). Interestingly, associations for consumption of the outer bran portion of the kernel, but not germ intake, were comparable to those of whole grain intake.

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Potential effects of DF consumption. Colonic fermentation with the production of SCFA can be observed with most types of DF to some extent, but it tends to be more pronounced with soluble DF in naturally available foods.

A causal relationship can not be stated, and estimation of food intake on the basis of semiquantitative FFQ is a known limitation (2). Moreover, even after statistical adjustment for potentially confounding factors, residual confounding by additional unmeasured or inaccurately measured factors can not be excluded. However, the consistency of the results clearly indicates that the consumption of insoluble cereal DF could play an important role in the prevention of diabetes.

Potential mechanisms

DF, satiety, and body weight. Potential mechanisms that indicate DF consumption might alter diabetes risk include effects on satiety and body weight. A number of studies showed increased postprandial satiety or decreased subsequent hunger when subjects consumed high DF diets, both under conditions of fixed energy intake and when energy intake was consumed ad libitum (7). However, other studies reported no significant effects (7–10). Not all studies (11) showed an inverse association between postprandial glucose and insulin responses and satiety, and no clear conclusion can be drawn that low vs. high glycemic index meals are a key factor promoting satiety (12).

Most (7), but not all (13), observational studies showed an inverse, sometimes dose-dependent (14) relationship between DF consumption and body weight. Effects were moderate, with individuals in the highest quintile vs. lowest quintile of DF consumption gaining 3.6 kg less over a 10-y period (14). Several (7), but not all (9,15), relatively short-term interventions further indicate that moderate reductions of body weight can be achieved with high DF diets.

Generally, in human studies, no clear difference regarding weight gain has been shown between soluble and insoluble DF and fermentable and nonfermentable DF, or between foods naturally high in DF and fiber supplements (7). Therefore, reduced body weight in subjects consuming high DF diets is likely to contribute to reduced diabetes risk, but it cannot explain the observed stronger associations for insoluble DF.

DF and hormonal responses. DF consumption affects the secretion of various gut hormones that may act as satiety factors (8,16–19). However, in many of the experiments in humans, hormonal changes were not linked to acute feelings of satiety. A guar gum DF supplement produced a heightened postprandial cholecystokinin response, but did not alter satiety ratings (16). Insoluble wheat DF-induced changes of orexigenic ghrelin and anorexigenic peptide YY (PYY) were not associated with acute changes in hunger and satiety (8) but may have affected satiety upon the consumption of a subsequent meal (8,20). Highly fermentable DF increase glucagon-like peptide 1 levels and may play a role in the regulation of postprandial satiety in diverse animal species. However, in humans, no fiber-induced changes of circulating glucagon-like peptide 1 levels have been observed (17,18,21), and ingestion of a fermentable (pectin, β-glucan) vs. a nonfermentable (methylcellulose) DF supplement was found to be less, rather than more, satiating (9). Glucose dependent insulinovertic polypeptide (GIP) is another incretin hormone that appears to be involved in the regulation of fat metabolism. Effects of DF consumption on circulating GIP yielded mixed results. Soluble DF reduced circulating GIP in diabetic humans (19), probably because of reduced carbohydrate absorption, whereas insoluble cereal DF consumption yielded accelerated responses of both biologically active GIP (17) and insulin (17,22) in healthy subjects. In a cross-sectional analysis, high intakes of cereal DF were positively associated with plasma adiponectin after adjusting for lifestyle factors and dietary glycemic load (23). Adiponectin may act as a peripheral starvation signal promoting the storage of triglycerides preferentially in adipose tissue (24). As a consequence, reduced triglyceride accumulation in the liver and in the skeletal muscle might convey improved systemic insulin sensitivity (25). In summary, various changes in circulating concentrations of gut and adipocyte-derived hormones can be observed in humans that ingest a high DF diet. However, no obvious mechanism can be derived explaining stronger associations for insoluble DF with diabetes risk.

DF and insulin sensitivity. An increased intake of total DF was inversely associated with markers of insulin resistance in several studies (26). Investigating different sorts of soluble and insoluble DF in randomized controlled intervention studies yielded mixed results. Consumption of wheat bran for 3 mo did not change fasting glucose and glycated hemoglobin (HbA1c) levels in diabetic subjects (27). High DF rye bread enhanced insulin secretion but did not appear to improve insulin sensitivity in postmenopausal women, as estimated with the frequently sampled intravenous-glucose-tolerance test (28). However, using a second meal test design, improved markers of insulin resistance have been reported after consumption of various other sorts of insoluble DF (17,18,20,29). When measuring insulin sensitivity using euglycemic-hyperinsulinenic clamps, consumption of insoluble DF increased whole body glucose disposal independent of changes in body weight in both short-term and more prolonged studies (21,30,31). Insulin resistant subjects are more likely to eventually develop diabetes. Therefore, improved insulin sensitivity could be a relevant factor contributing to reduced diabetes risk in subjects consuming diets high in insoluble DF.

DF and inflammation. Recent studies show reductions of inflammatory markers in subjects consuming high DF diets (32). Inter-
Estingly, some sorts of DF have been reported to bind to specific receptors on immune cells, suggesting a direct immune-modulatory effect (5). Other potentially involved mechanisms might include weight loss when consuming high DF diets, as well as antihyperglycemic effects and effects on lipid oxidation (32). Both a diet high in total DF and consumption of a soluble DF supplement significantly decreased levels of the inflammatory marker C-reactive protein (33). Fermentation of soluble DF may also play a role due to potential antiinflammatory properties of butyrate (32). However, reductions in inflammatory markers have been reported to be comparable with both insoluble DF and more readily fermentable soluble DF (34).

Colonic fermentation and gut bacteria. Short-chain fatty acids (SCFA) such as acetate, propionate, and butyrate are produced by bacterial fermentation of indigestible DF polysaccharides in the colon (1), with the proportion of different SCFA not being fixed, depending on the substrate and eventually on the gut microflora. Commonly, increased production of SCFA is assumed to be beneficial by reducing hepatic glucose output and improving lipid homeostasis (32). Further, G protein-coupled receptors (GPR)-41 and GPR43 function as direct targets of SCFA. An interesting finding was that oral administration of the GPR41 ligand propionate almost doubled plasma concentrations of anorexigenic leptin in mice, even though no effect on food intake was detected (35).

However, data not unequivocally indicate that fermentability of DF per se is a key factor contributing to reduced diabetes risk. Consumption of low fermentable cereal DF (corn and wheat) show stronger associations with reduced diabetes risk than more readily fermentable soluble DF from fruit and vegetables (2,3). When investigating effects of weakly fermentable insoluble cereal DF and highly fermentable resistant starch in a randomized controlled cross-over study in healthy women (17), markers of insulin sensitivity in a second meal test were improved to a similar extent with all DF, independent of the rate of colonic fermentation (Fig. 2). These experiments indicate that a dose-dependent relation between fermentability of DF and improved markers of insulin sensitivity was unlikely, even though the limited accuracy of the available methods to estimate colonic fermentation rates in humans must be considered (4). Further, SCFA might stimulate adipogenesis through GPR43 (35), and colonization of germ-free (gnotobiotic) mice with a prominent saccharolytic member of the normal human gut microbiota, together with the dominant human methane producing germ, resulted in markedly improved efficacy of colonic fermentation, associated with increased de novo lipogenesis and obesity in the host (36). However, it needs to be emphasized that nutritional habits and physiological effects of DF intake in rodents and humans largely differ, with rodents recovering energy from coprophagia (4). In humans, SCFA account for <10% of daily energy intake (37).

DF consumption might affect further factors linking the gut microbiota with obesity and insulin resistance. Obese subjects have a different composition of the gut microbiota than lean subjects, and changes toward the “lean microbiota” can be observed in obese subjects that lose weight [referenced in (36)]. When transplanting the gut microbiota from obese mice or from lean mice to germ-free mice, the recipients of the “obese microbes” showed an increased gain of fat mass, even though energy intake was comparable (36). Interestingly, a high DF diet (oligofructose) reduced gram-negative bacterial content and body weight, whereas a high fat diet increased the proportion of a gram-negative bacterial lipopolysaccharides (LPS) containing microbiota in humans [referenced in (38)]. Continuous subcutaneous infusion of LPS for 4 wk increased weight gain, liver fat, inflammatory markers, and markers of insulin resistance to a similar extent than...
a high-fat diet (38). These studies indicate that DF consumption could have the potential to influence the proportions of certain members of the gut flora, thus linking the concepts of bacterial colonization, inflammation, and insulin resistance.

Prospective cohort studies indicate that diets high in insoluble cereal DF and whole grains might reduce diabetes risk. In contrast, there is no strong support that soluble DF from fruits and vegetables play a key role in this context. Many of the proposed protective mechanisms of DF consumption are either shared by soluble and insoluble DF (moderate weight loss, low energy density, increased satiety, effects on inflammatory markers and gut hormones), or they are more likely to be relevant with soluble viscous DF consumption (hindering of macronutrient absorption, slowing of gastric emptying, reduced postprandial glucose responses, reduced total and LDL cholesterol, and colonic fermentation). Therefore, other unknown mechanisms appear to be involved in conveying reduced diabetes risk in subjects consuming diets high in insoluble cereal DF. A promising factor contributing to beneficial effects of insoluble DF consumption could be increased insulin sensitivity, even though mechanisms leading to this phenomenon need to be defined. Hypothetical mechanisms include a shift in the relation of gut microbiotic communities, as well as direct and indirect influences on yet unknown hormonal and molecular factors in the host that may be altered in subjects consuming high DF diets.

Literature Cited