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REVIEW

Dietary Fiber, Gut Peptides, and Adipocytokines

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ABSTRACT The consumption of dietary fiber (DF) has increased since it was related to the prevention of a range of illnesses and pathological conditions. DF can modify some gut hormones that regulate satiety and energy intake, thus also affecting lipid metabolism and energy expenditure. Among these gut hormones are ghrelin, glucagon-like peptide 1, peptide YY, and cholecystokinin. Adipose tissue is known to express and secrete a variety of products known as ''adipocytokines,'' which are also affected by DF. Some of the most relevant adipocytokines include adiponectin, leptin, tumor necrosis factor-α, and interleukin-6. The release of adipocytokines, by either adipocytes or macrophage-infiltrated adipose tissue, leads to a chronic subinflammatory state that could play a central role in the development of insulin resistance and type 2 diabetes, therefore increasing the risk of cardiovascular disease associated with obesity. DF modulation of these molecules could also have positive effects on obesity, insulin resistance, and hyperlipidemia. This review is focused on the effects of DF on the above-mentioned gut peptides and adipocytokines.

KEY WORDS: • ***cytokines*** • ***fibers*** • ***peptides***

INTRODUCTION

It is well-established that nutrition can have a direct impact on normal physiological functions, as well as on pathological conditions such as obesity, diabetes, and cardiovascular disease. Dietary fiber (DF) is actually a group of components in foods of vegetable origin (cereal, fruit, vegetables, and legumes) that are not broken down by human digestive enzymes.[1,2] DF is introduced at weaning and consumed into adulthood, and elevated levels have been demonstrated to be particularly protective against increased body fat and glycemic dysregulation, even when a high-energy diet is consumed.[3] Nevertheless, the mechanisms involved in the health-promoting effects of DF are unclear.

DF can be subdivided or classified into insoluble and soluble DF. As its name suggests, insoluble DF is made up of substances that do not dissolve in water (cellulose, hemicellulose, lignin, and resistant starch). Its components resist the action of intestinal microorganisms, and thus it can therefore be classed as non-fermentable. Soluble DF is composed of water-soluble elements with a gel-forming capacity (inulin, pectins, gums, and fructo-oligosaccharides) that give volume to feces. These substances predominate in legumes, cereals (oats and barley), and some fruits and are used by intestinal microorganisms, especially colonic flora. This type of DF is therefore also known as fermentable DF.[4] Reducing saturated fat and cholesterol intake while increasing unsaturated fat intake is a well-known healthy dietary objective, but the importance of other dietary approaches, such as increasing soluble DF intake, is nowadays increasingly recognized.[5]

Generally, the beneficial effects of DF could be due to its actions in the digestive tract. Soluble DF delays glucose and fat absorption, giving it an anti-obesity effect. It also influences postprandial glycemia and insulinemia and has hypolipidemic effects.[6] Furthermore, soluble DF fermentation by colonic microflora leads to the formation of short-chain fatty acids (acetic, propionic, and butyric acids) that are associated with the prevention of cardiovascular disease, colorectal cancer, and inflammation.[6] In addition, DF can affect food intake by modulating the production of gut hormones that are involved in appetite regulation. It specifically affects the orexigenic peptide ghrelin and some anorexigenic hormones such as glucagon-like peptide-1 (GLP-1), peptide YY (PYY), and cholecystokinin (CCK). These hormones would also affect lipid metabolism and energy expenditure, thus influencing body weight.[6,7]

Adipose tissue has been traditionally considered an energy storage depot with few interesting attributes. Because of the dramatic rise in obesity and its metabolic sequelae over the past decades, adipose tissue has garnered tremendous scientific interest.[8] In fact, adipose tissue is now known to be an active metabolic tissue that secretes multiple metabolically important proteins known as ''adipocytokines.''[9] These adipose tissue-derived factors play a central role in whole body homeostasis by influencing a variety of biological and

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physiological variables and processes, including food intake, energy balance, insulin action, lipid and glucose metabolisms, angiogenesis and vascular remodeling, blood pressure, and coagulation.[10] DF modulation of adipocytokines could also have positive effects on several pathologies, including obesity, insulin resistance, and hyperlipidemia.

Bearing in mind the different experimental studies demonstrating the benefits of DF on health, especially obesity, the present review attempts to bring together the most important findings of the current research in this field, concentrating in particular on the effects of DF on the most relevant gut peptides and the adipocytokines with key roles in cardiometabolic diseases.

DIETARY FIBER AND GUT PEPTIDES

Ghrelin

Ghrelin, a 28-amino-acid peptide mainly produced in the stomach mucosa, was identified in 1999 as the endogenous ligand for the growth hormone secretagogue receptor.[11] Subsequently circulating ghrelin levels were found to increase under conditions that correlate with hunger in humans,[12] and ghrelin administration induced eating in both rats[13] and humans.[14] In addition to promoting growth hormone secretion, ghrelin is the only known circulating orexigenic compound and, consequently, has received substantial attention as an important factor in regulating mammalian hunger and energy balance. Ghrelin is produced in many different tissues, including the brain, pituitary, gonads, intestine, pancreas, lymphocytes, placenta, kidney, and lung. However, more than 65% of circulating ghrelin is released by the stomach mucosa. In addition to its hormonal function, ghrelin is also thought to have local autocrine/paracrine actions helping to regulate processes such as cell proliferation, adipogenesis, cardiovascular function, gastric secretion and motility, glucose metabolism, and insulin production.[15]

It has been reported that fermentable fibers like fructans are rapidly and extensively fermented in the proximal part of the colon and may potentially modulate ghrelin levels.[16] Very recently, it has been reported that the plasma ghrelin levels were 23% lower after consumption of 3% β-glucan-enriched bread compared with a control normal bread.[17] Moreover, it has also been demonstrated that psyllium-enriched meals decreased ghrelin response in healthy young adults.[18] Under fasting conditions, St-Pierre *et al.*[19] also observed positive associations between fiber intake and total and acylated ghrelin levels. Their study suggested that fiber intake is an important regulator of ghrelin levels both in fasting and in hyperinsulinemic conditions in overweight and obese postmenopausal women. Recently, other studies reported that fermentable fiber inulin reduces ghrelin levels in healthy subjects. According to Tarini and Wolever,[20] the mechanisms implicated in the fiber effects could be related with the increase in content of short-chain fatty acids and the reduction in levels of free fatty acids in the colon, something that could attenuate type 2 diabetes. These researchers also proposed that these fiber effects are in turn related with ghrelin levels and regulate food intake.

GLP-1

GLP-1 is a gut-secreted peptide that has been proposed as a potential antidiabetes/anti-obesity drug. This hormone is also naturally secreted in response to meal ingestion, but it is degraded rapidly after endogenous secretion or exogenous injection.[21] GLP-1 has been shown to mediate central nervous system effects relating to satiety[22] and cognition.[23]

The effect of DF on GLP-1 has been known for a long time ago. In 1996, a diet supplemented with fiber was reported to significantly modulate GLP-1. This novel finding suggested a beneficial role for fiber in improving glucose homeostasis.[24]

In 1998, it was reported that the ingestion of fermentable fibers by healthy dogs for 14 days was associated with greater GLP-1 secretion and smaller oscillations in postprandial blood glucose concentrations.[25] In the same year, another research group demonstrated that cecal cell proliferation induced by oligofructose leads to increase GLP-1 concentrations in male Wistar rats fed a diet with or without 10% oligofructose for 30 days.[26] More recently, it has been reported that oligofructose supplementation also improved glucose homeostasis in diabetic rats previously treated with streptozotocin. This phenomenon was partly linked to a reduction in food intake and was correlated with the increase in colonic and portal GLP-1 content.[27] Later, it was demonstrated that the inclusion of high amylose-resistant cornstarch in the diet may affect the energy balance through its effect as a DF stimulator of GLP-1 expression, suggesting that this increase in gut hormone signaling may be an effective natural approach to the treatment of obesity.[28] Zhou *et al.*[21] provided strong evidence that dietary resistant starch up-regulated total GLP-1 in a sustained day-long manner in rodents. These increases were associated with the fermentation of the fiber in the lower intestine.[21] Very recent studies have also revealed that high DF levels increase plasma GLP-1 compared with levels in animals consuming control and high-protein diets. In addition, direct evidence exists that fermentation products increased GLP-1 expression *in vitro*.[21]

PYY

PYY is a 36-residue gastrointestinal peptide primarily synthesized in isolated mucosal endocrine cells scattered through the colon and the ileum.[29] Release of PYY is stimulated by nutritive factors, in particular, the presence of fat in the ileum and colon, and it is known that PYY inhibits both pancreatic and gastric secretion.[30] PYY has been proposed as a potential antidiabetes/obesity hormone, and recent studies have demonstrated a relation between DF intake and these pathologies.

When a 14-week treatment of Viscofiber (Cevena Bioproducts Inc., Edmonton, AB, Canada) obtained from oats and barley (4 g/day) was combined with a lifestyle change program, weight loss and an increase in fasting PYY levels were observed.[31] In addition, the short-term consumption of β-glucans from barley was able to control appetite by modulating sensations and reducing energy intake, and the researchers suggested that the satiety effect of β-glucans may

be mediated by an increase of PYY.[17] In this context, Beck *et al*.[32] also demonstrated that an increase in the dose of β-glucan produced significantly higher levels of plasma PYY at 2–4 hours after consumption. Short-chain fatty acids directly increased PYY promoter activity in an *in vitro* study.[28] It was reported that PYY mRNA expression was higher in the cecum and colon of resistant starch-treated rats. It is interesting that dietary resistant starch did not affect PYY gene expression in the ileum, although the highest non-induced expressions for these genes were detected in the ileum. Thus, the stimulating factor that specifically responds to dietary resistant starch might only exist in the lower intestine, where resistant starch ferments to produce short-chain fatty acids.[21]

CCK

CCK is one of the first gastrointestinal hormones to be discovered, and it is one of the most abundant neuropeptides in the brain. It was originally isolated from porcine duodenum as a 33-amino-acid peptide.[33,34] Major biological actions of CCK are the reduction of food intake and the induction of anxiety-related behavior.[35]

It has been demonstrated that there is a link between the intake of DF and the increase of CCK. In 1992, nine healthy male volunteers received three different isocaloric diets via intraduodenal perfusion; the highest CCK plasma values were observed in those fed a high-molecular diet enriched with fat and fiber.[36] Other researchers evaluated the effects of a completely soluble fiber on fasting and postprandial CCK hormone levels in 25 obese but otherwise healthy females; the results indicated that a hydrolyzed guar gum fiber supplement produced a heightened postprandial CCK response.[37] Moreover, when 11 healthy men were fed barley-containing meals, CCK remained elevated for a longer time after the intake.[38] Nevertheless, this same research group later performed another study in which men consumed beans as a source of DF and a control meal in random order, and the CCK response was twice as high after the bean-containing meal than after the control meal.[39] Recently, it has been observed that β-glucan improved satiety, and the release of CCK is probably part of the mechanism implicated in this effect.[40] Burton-Freeman *et al*.[41] in 2002 suggested that the properties of fibers that prolong the exposure of meal contents, in particular dietary fat, to the intestinal mucosa could contribute to the increase in subjective satiety during the postmeal period, and it has been postulated that these effects of DF on satiety may be mediated, at least in part, through prolonged release of CCK.

Effects on the four gut peptides discussed here are summarized in Table 1.

Table 1. Effects of Dietary Fiber on Gut Peptides

Effect	*Fiber*	*Reference*
↑Ghrelin	Fructans	Wang *et al*.[16]
	Psyllium	Karhunen *et al*.[18]
	β-Glucan	Vitaglione *et al*.[17]
↑Glucagon-like factor-1	Fermentable plant fibers	Massimino *et al*.[25]
	Resistant starch	Zhou *et al*.[21]
	Inulin/oligofructose	DeVries *et al*.[1]
↑Peptide YY	β-Glucan	Vitaglione *et al*.[17] Beck *et al*.[32]
↑Cholecystokinin	Oat and barley Viscofiber	Greenway *et al*.[31]
	Dry beans	Bourdon *et al*.[38]
	β-Glucan	Beck *et al*.[32]

DIETARY FIBER AND ADIPOCYTOKINES

Adiponectin

Adiponectin is an abundant multifunctional adipocyte-derived protein with anti-inflammatory, anti-atherogenic, and insulin-sensitizing activity.[42] Adiponectin has sequence homology to the C1q family of complement proteins and circulates in low-, medium-, and high-molecular-weight forms. Clinical data indicate that the high-molecular-weight form strongly correlates with improved insulin sensitivity and glucose tolerance, whereas the association of total adiponectin levels with these factors is not as strong.[43] Adiponectin levels have been shown to be lower in males, obesity, insulin resistance, patients with type 2 diabetes mellitus, coronary artery disease, and essential hypertension.[44–48] In addition, it is known that there is a link between the diet and the levels of this adipocytokine because it has been demonstrated that adiponectin concentrations decrease transiently after consumption of a high-carbohydrate, low-fiber meal.[49]

Several studies have demonstrated that adiponectin levels are increased with DF intake. Galisteo *et al*.[50] observed that prolonged feeding with a 3.5% *Plantago ovata* husk-supplemented diet prevents endothelial dysfunction and the development of hypertension in obese Zucker rats, effects that are accompanied by a decrease in body weight gain, reduced hyperinsulinemia and dyslipidemia, and restoration of plasma adiponectin concentration. A cross-sectional analysis in women with type 2 diabetes revealed that the intake of cereal fiber and fruit fiber was significantly associated with increasing plasma adiponectin concentrations. These data indicate that dietary cereal fiber as well as the glycemic load and the glycemic index are associated with circulating adiponectin concentrations in humans.[51] However, these associations were not modified by obesity status.[52] Recently, Yannakoulia *et al*.[53] indicated that a dietary pattern characterized by high consumption of whole-grain cereals was significantly, yet modestly, positively related to circulating adiponectin concentrations; they observed that a potential beneficial effect on adiponectin levels could induce health benefits not only on the insulin and glucose metabolism, but also on changes in inflammatory markers or other adipocytokines. In this sense, in cultured cells, adiponectin has been shown to reverse the deleterious effects of tumor necrosis factor-α (TNF-α) and other cytokines on endothelial function. TNF-α-induced expression of several adhesion molecules, including vascular cell adhesion molecule-1, E-selectin, and intercellular adhesion molecule-1, was blocked by adiponectin.[54,55] Nilsson *et al*.[56] reported that an evening meal consisting of kernel-based barley bread

resulted in higher concentrations of adiponectin the following morning compared with a wheat flour bread, indicating anti-inflammatory properties from the ordinary barley kernel bread product. Our research group has evaluated the adiponectin plasma levels in several groups of obese Zucker rats fed different fibers. The rats fed an apple pectin fiber, and particularly those fed a soluble cocoa fiber product, showed higher adiponectin plasma levels than the rats fed a standard diet.[57] Adiponectin plasma levels are therefore conditioned by DF ingestion and are important for health. In fact, adiponectin inhibits atherosclerosis, suggesting that this protein might prevent the onset and progression of cardiovascular diseases. It has been suggested that high-molecular-weight adiponectin is a useful marker for the evaluation and care of subjects with metabolic syndrome and related disorders.[58]

Leptin

Leptin is the protein product encoded by the obese (*ob*) gene. It is a circulating hormone primarily produced by adipose tissue.[59] Since its identification in 1994, leptin has attracted much attention as one of the most important signals for the regulation of food intake and energy homeostasis.[60–62] Leptin binds to its receptors in various regions of the central nervous system, including the hypothalamus and brainstem, where it activates neural pathways that decrease appetite and increase sympathetic nervous system activity and energy expenditure.[63,64] Although changes in food intake and total body fat can clearly affect insulin sensitivity in peripheral tissues, several observations suggest that leptin regulation of glucose homeostasis occurs independently of its effects on food intake through central and peripheral mechanisms.[8]

It is known that obesity in humans is associated with hyperleptinemia, and increased adiposity is believed to be associated with development of leptin resistance.[16] Some researchers have observed that in conditions of high-sugar/low-fiber, glucose and leptin levels decreased more slowly (glucose levels were still high at 60 minutes, and leptin levels at 90 minutes) than in a low-sugar/high-fiber condition.[65] Other researchers showed that circulating leptin was decreased after supplementation with DF-rich fungal chitosan and that this effect was related to lower fat mass development (adiposity index).[66] However, no effects of white bread rolls supplemented with 15 g of arabinoxylan for 6 weeks were observed on leptin levels in type 2 diabetic subjects.[67]

Pro-inflammatory cytokines

TNF-α. TNF-α, an inflammatory cytokine produced by macrophages/monocytes during acute inflammation, is responsible for the diverse range of signaling events within cells that lead to necrosis or apoptosis.[68] This cytokine is not secreted by adipocytes, but it is secreted by macrophages infiltrating adipose tissue, and it functions as a paracrine and/or autocrine factor.[69,70] TNF-α is suspected to play a role in obesity and concomitant metabolic disturbances, such as insulin resistance, and is one of the most important mediators of inflammation.[71,72]

The modulation of TNF-α levels after consumption of DF has been studied. Some researchers evaluated whether long-term intake of a fiber-supplemented diet (3.5% *P. ovata* husks) had preventive effects on the development of abnormalities in the experimental model of obese Zucker rats. Their results revealed reduced circulating concentrations of TNF-α in the animals treated with this fiber.[50] Another study affirmed that partially hydrolyzed guar gum inhibited increases in intestinal TNF-α protein and mRNA expression after dextran sulfate sodium administration in mice.[73] In addition, very recently, in 2010, Galisteo *et al.*[74] also observed that the increased TNF-α levels found in obese Zucker rats were significantly improved when these rats were fed a *P. ovata* husk-supplemented diet. Very recently, our research group has evaluated the TNF-α plasma levels in obese Zucker rats fed different fibers and has observed a decrease in this protein when the rats were fed β-glucan, apple pectin, or soluble cocoa fiber.[57] Many studies have suggested that a high-fiber diet might be a tool to reduce inflammation, and therefore a way to reduce diseases that are associated with increased inflammation. This is quite important because the identification of dietary factors that reduce inflammation could have undoubted significant public health implications for the prevention of diabetes mellitus, cardiovascular disease, and metabolic syndrome.[75]

There are several mechanisms to explain the possible positive effect of DF on inflammation. It is known that while a high-fat, high-carbohydrate meal induces oxidative stress and inflammation, including priming the transcription of genes for pro-inflammatory compounds like TNF-α, a meal rich in fiber and fruit does not. In addition, a high-fat, high-carbohydrate meal induces a concomitant increase in the plasma concentration of endotoxin and the expression of its specific receptor, Toll-like receptor-4. This combination provides a further pro-inflammatory mechanism that is relevant to subsequent meals because both of these effects last for more than 5 hours. In contrast, a meal rich in fiber and fruit does not induce these effects.[76]

Interleukin-6 and interleukin-8. Interleukin-6 (IL)-6 is a pro-inflammatory cytokine produced by several cells (fibroblasts, endothelial cells, monocytes) and adipose tissue, and its content is increased in obesity.[77,78] Approximately 30% of circulating IL-6 is derived from white adipose tissue, with visceral fat producing higher levels of IL-6 than subcutaneous fat.[79] In addition, plasma IL-6 is highly correlated with body mass and inversely related to insulin sensitivity.[80,81] IL-8 can also be synthesized in adipose tissue,[82] and this pro-inflammatory cytokine is also implicated in the development of insulin resistance. In particular, in obese subjects, IL-8 concentrations are correlated inversely with insulin sensitivity.[83]

The intake of carbohydrate and fiber modulates inflammation. In fact, a prolonged postprandial inflammatory response after high-fat, high-carbohydrate meals has been described in obese individuals.[84] In contrast, DF has been related to a decrease in pro-inflammatory cytokine levels and may acutely reduce inflammatory activity.[49] Nilsson *et al.*[56] demonstrated in 2008 the anti-inflammatory

properties of a kernel-based barley bread administered in the evening meal. The intake of this bread resulted in lower concentrations of IL-6 the following morning compared with a wheat flour bread in the evening meal. Another study, carried out by Manning *et al*.[85] in 2008, indicated that plasma IL-6 concentrations increased to levels substantially above baseline in the late postprandial period after meals rich in high glycemic index carbohydrates with and without fat and after ingestion of low glycemic index, high DF carbohydrates. This response of plasma IL-6 to the meals was markedly higher in obese women than in lean women and was lower after ingestion of low glycemic index, high DF carbohydrates than that of high glycemic index, low DF carbohydrates. Therefore, according to these researchers, obesity enhances the postprandial increase in IL-6 in women irrespective of the type or content of fat in the meal, and DF attenuates this increase insofar as IL-6 is concerned.[85] In another study, total DF intake was also significantly and inversely associated with different inflammation markers, such as IL-6, in nondiabetic men (60–79 years old) followed for 7 years.[86] It has been also demonstrated that after consumption of a diet supplemented with 5% fungal chitosan for 10 weeks the IL-6 levels decreased in the serum of obese mice.[66] In addition, Sofi *et al*.[87] have also indicated in 2010 that the short-term dietary intake of a whole grain bread obtained from an old grain variety lowers circulating levels of atherosclerosis markers such as IL-8. Moreover, butyrate, one of the major metabolites of dietary fiber, dose-dependently inhibited TNF-α and IL-8 secretion in the human intestinal epithelial cell line HT-29.[88]

In the context of all these ideas, it is important to keep in mind that inflammation may be a mechanism through which high postprandial insulin and glucose responses increase the risk of type 2 diabetes mellitus.[89] An increased intake of total DF was inversely associated with markers of insulin resistance,[90] and consumption of soluble DF reduces the postprandial glucose response after carbohydrate-rich meals.[91] Colonic fermentation with the production of short-chain fatty acids 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.[92] Commonly, increased production of short-chain fatty acids is assumed to be beneficial in that it reduces hepatic glucose output and improves lipid homeostasis.[93] Nevertheless, it is not soluble DF, but rather the consumption of insoluble cereal DF and whole grains, that has been consistently associated with a reduced risk of type 2 diabetes in large prospective cohort studies.[94,95]

After a high-carbohydrate meal, DF could therefore reduce the increased postprandial levels of pro-inflammatory cytokines that are inversely correlated with insulin sensitivity. The mechanisms responsible for the anti-inflammatory and antidiabetic effects of dietary fiber have not yet been completely elucidated, but, in any case, our meals and eating patterns in today's modern society are partial to high-fat, high-carbohydrate pro-inflammatory meals, which are low in fiber, and the effects of diets rich in fiber appear beneficial from the view point of the prevention of diabetes as well as inflammation.[76]

Table 2. Effects of Dietary Fiber on Adipocytokines

Effect	*Fiber*	*Reference*
↑Adiponectin	*P. ovata*	Galisteo *et al*.[50]
	Cereal and fruit fiber	Qi *et al*.[51]
	Whole-grain cereals	Yannakoulia *et al*.[53]
	Kernel-based barley bread	Okamoto *et al*.[55]
	Apple pectin and cocoa fiber	Sánchez *et al*.[57]
↓Leptin	Fungal chitosan	Neyrinck *et al*.[66]
↓Tumor necrosis factor-α	*P. ovata*	Galisteo *et al*.[50,74]
	Guar gum	Naito *et al*.[73]
	Apple pectin and cocoa fiber	Sánchez *et al*.[57]
↓Interleukin 6	Kernel-based barley bread	Nilsson *et al*.[56]
	Fungal chitosan	Neyrinck *et al*.[66]

Effects on the four adipocytokines discussed here are summarized in Table 2.

CONCLUSIONS

In this review, we have described the beneficial effects of DF on different gut peptides and adipocytokines. In fact, all of the above-mentioned information allows us to conclude that the bioactive effects of DF are, at least in part, mediated by the modification of gut peptides and adipocytokines. The inclusion of easily consumed fiber as part of our daily diet, in appropriate quantities, could be a very attractive strategy to improve health. DF could be used as a functional food ingredient. However, further studies focused on elucidating the molecular mechanisms and the intracellular signaling pathways involved in the different DF effects are needed.

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AUTHOR DISCLOSURE STATEMENT

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