

Fiber intake Inconsistently Alters Gut Hormone Levels in Humans Following Acute or Chronic Intake

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Abstract

Diet composition affects the release of gut hormones involved in the regulation of appetite and energy intake. While some research suggests high fiber foods cause greater satiety than low fiber foods, few studies have measured gut hormone levels as a mechanism by which fiber may influence appetite. A review of the literature was conducted to better understand the effect of fiber on gut hormone concentrations in humans, which specific focus on peptide YY, glucagon-like peptide-1, cholecystokinin, and ghrelin. Considerable variation was found in study design, population, fiber type and level. Few studies reported a significant effect of fiber on gut hormone levels, and data suggest caloric load may have a more significant influence on gut hormone release. While it is possible that circulating gut hormones are not the mechanism by which fibers influence satiety, it is also possible that variability in study design prevents definitive conclusions around this relationship.

Keywords: Dietary fiber, Peptides, Gut hormones, Cholecystokinin, Ghrelin, Glucagon-like peptide-1, Peptide YY

1. Introduction

A variety of peptides are released from the gastrointestinal (GI) tract in response to the nutritional state. These gut hormones are considered to be important factors in the control of appetite and satiety. The strength and timing of postprandial gut hormone release is clearly influenced by macronutrient distribution and total meal composition. Certain macronutrients are thought to be more satiating due to their ability to influence gut hormones; however, the impact of fiber on this relationship is not clearly understood. While some research suggests high fiber foods result in greater satiety than low fiber foods, few studies have measured circulating gut hormone response after fiber intake in humans. Therefore, a review of the literature was conducted to better understand fibers' impact on gut hormone concentrations in the blood. Although many peptides and hormones are released from cells in the GI tract and may influence satiety (e.g. oxyntomodulin, pancreatic polypeptide, glucose-dependent insulinotropic polypeptide, leptin, adiponectin, enterostatin, glucagon, insulin, amylin), only

four – peptide YY (PYY), glucagon-like peptide-1 (GLP-1), cholecystokinin (CCK), and ghrelin – were chosen for this review due to their relatively well established effects on appetite.

1.1 Peptide YY

PYY is a 36-amino-acid polypeptide synthesized and secreted from the L-cells of the terminal ileum (Batterham *et al.*, 2007). Upon release, the molecule undergoes cleavage by the enzyme dipeptidyl peptidase IV (DPP-IV) to yield a truncated peptide, PYY3-36, which is the predominant circulating form in the fed and fasted state (Sloth, Davidsen, Holst, Flint, & Astrup, 2007). PYY3-36 binds with high affinity to the Y2 receptor, located throughout the central nervous system (CNS) and vagal afferents (Neary *et al.*, 2005). PYY is thought to inhibit appetite by acting centrally on homeostatic centers in the hypothalamus to reduce expression of neuropeptide Y (NPY), an orexigenic peptide. Neural reflexes are also important, since PYY concentrations increase before nutrients reach the site of PYY release and vagotomy abolishes the appetite suppressing effect of PYY (Abbott *et al.*, 2005). PYY also activates the ileal brake, which slows gastric emptying and nutrient absorption, and may extend feelings of satiety (Maljaars, Peters, Mela & Masclee, 2008).

Plasma PYY levels rise within 15 minutes of a meal, and peak approximately an hour after nutrient ingestion (Adrian *et al.*, 1985). The magnitude of PYY release depends on both the caloric load and macronutrient content of the meal. When balanced for total energy, meals high in fat and protein appear to increase PYY more than carbohydrate-rich meals (Batterham *et al.*, 2006; Essah, Levy, Sistrun, Kelly & Nestler, 2007; MacIntosh *et al.*, 1999). Intravenous infusion of PYY has been shown to significantly increase satiety and reduce energy intake in humans (Batterham *et al.*, 2002; Batterham *et al.*, 2003; Batterham *et al.*, 2007; Degen *et al.*, 2005). However, many studies use pharmacological doses which can lead to side effects such as nausea and vomiting, which may interfere with appetite ratings. Researchers have reported lower fasting and postprandial PYY concentrations in obese participants compared to lean individuals, and this is reversed following bariatric surgery (Batterham *et al.*, 2003; le Roux *et al.*, 2006). This suggests PYY may play an important role in energy homeostasis, and has led to interest in PYY as a potential antiobesity therapeutic agent.

1.2 Glucagon-like peptide-1

GLP-1 is formed from the cleavage of proglucagon, and is released primarily from the L-cells of the distal small intestine. Further N-terminal truncation is required to produce the biologically active form, GLP-17-36 (Chaudhri, Small & Bloom, 2006). GLP-1 undergoes rapid degradation by DPP-IV and only 10-15% reaches the systemic circulation intact (Holst, 2007). GLP-1 receptors are expressed in the gut, brainstem, hypothalamus, and vagal afferent nerves. It is thought that GLP-1 may access the CNS directly via the area postrema, which lacks a blood-brain barrier, but the significance of this pathway is unknown (Dhillon & Bloom, 2004). GLP-1 exerts several physiological effects that may influence appetite. As an incretin hormone, GLP-1 amplifies the insulin response to glucose ingestion and inhibits the release of glycogen from the liver (Baggio & Drucker, 2007; Cummings & Overduin, 2007; Huda, Wilding & Pinkney, 2006). In the GI tract, GLP-1 inhibits gastric and pancreatic exocrine secretion, as well as gastric emptying, which may enhance satiety (Cummings & Overduin, 2007; Huda *et al.*, 2006; Naslund, Bogefors *et al.*, 1999).

Upon eating, plasma GLP-1 levels increase within 10-15 minutes and peak by 40 minutes (Orskov, Wettergren & Holst, 1996). This initial increase occurs prior to nutrients reaching the small intestine, and is likely mediated by neural inputs. GLP-1 release is proportionate to the number of calories consumed. Additionally, when matched for energy, meals high in carbohydrates and protein seem to be more potent stimulators of GLP-1 secretion than high fat meals (Bowen, Noakes, Trenerry & Clifton, 2006; Raben, Agerholm-Larsen, Flint, Holst & Astrup, 2003). In humans, GLP-1 infusion has been shown to increase satiety and decrease food intake in healthy normal weight and obese participants, as well as individuals with type 2 diabetes (Flint, Raben, Astrup & Holst, 1998; Gutniak *et al.*, 1997; Naslund *et al.*, 1999; Verdich *et al.*, 2001). A meta-analysis by Verdich *et al.* concluded that infusion with physiological doses of GLP-1 reduced energy intake by an average of 12% (Verdich *et al.*, 2001).

1.3 Cholecystokinin

CCK is released primarily from I-cells in the duodenum and proximal jejunum, but small amounts are also produced by neurons in the GI tract and nervous system (Liddle, 1997; Rehfeld, 2004). CCK is formed by selective processing of its precursor, proCCK, which results in multiple bioactive forms ranging in size from 8 to 58 amino acids (Reeve, Eysselein, Walsh, Ben-Avram & Shively, 1986; Rehfeld & Hansen, 1986). All isoforms show affinity for the CCK receptor, located on the gallbladder, pancreas, and stomach, as well as in the hindbrain and hypothalamus (Rehfeld, Sun, Christensen & Hillingsø, 2001). CCK-induced satiation appears to be mediated neuronally via activation of vagal afferents in the stomach and duodenum (Kopin *et al.*, 1999). In

addition, CCK slows gastric emptying, which may increase stomach distension and causes greater satiety (Liddle, Morita, Conrad & Williams, 1986).

Plasma CCK typically increases within 15 minutes of a meal, and the duration of elevation depends both on caloric load and macronutrient content. When matched for energy, fat and protein appear to be stronger stimuli for CCK release than carbohydrates (Liddle, 1997). In humans, infusion with CCK reduces meal size and duration, and has been estimated to suppress energy intake by an average of 22.5% (de Graaf, Blom, Smeets, Stafleu & Hendriks, 2004). There also appear to be gender differences in the CCK response, with women experiencing greater CCK elevation than men; however, it is not clear if this corresponds to differences in appetite sensations between genders (Nolan, Guss, Liddle, Pi-Sunyer & Kissileff, 2003; Schneeman, Burton-Freeman & Davis, 2003).

1.4 Ghrelin

Ghrelin is a 28-amino-acid peptide hormone originating primarily from the stomach, with lesser amounts formed in the small intestine and other organs (Kojima *et al.*, 1999). Circulating ghrelin is present in both an acylated and non-acylated form, but only the acylated form binds the ghrelin receptor and is considered biologically active (van der Lely, Tschop, Heiman & Ghigo, 2004). Ghrelin receptors are widely distributed throughout the body in tissues such as brain, stomach, intestine, pancreas, and heart (Cummings, 2006). Ghrelin is thought to interact with NPY and agouti-related peptide (AgRP)-expressing neurons of the arcuate nucleus of the hypothalamus through vagal afferents or more directly via the bloodstream (Huda *et al.*, 2006). NPY and AgRP are orexigenic peptides and promote food intake (Huda *et al.*, 2006).

Ghrelin is unique in that it is the only peripheral hormone known to be a powerful stimulant of appetite and food intake (Cummings & Overduin, 2007). Plasma ghrelin levels increase markedly prior to a meal, suggesting a role in meal initiation (Cummings *et al.*, 2001). In general, nutrient intake suppresses plasma ghrelin levels. While caloric load is the most important determinant of the magnitude and duration of ghrelin suppression, macronutrient composition of the meal also plays a role. When matched for total energy, lipids appear to be less effective than carbohydrates or protein at suppressing ghrelin (Al Awar, Obeid, Hwalla & Azar, 2005; Monteleone, Bencivenga, Longobardi, Serritella & Maj, 2003; Tannous dit El Khoury, Obeid, Azar & Hwalla, 2006). Peripheral infusion with ghrelin increases energy intake and hunger in humans (Wren *et al.*, 2001). In addition, there is evidence that obese individuals may be more sensitive to the effects of ghrelin (Druce *et al.*, 2005). Ghrelin may also play a role in long-term weight regulation as levels increase with weight loss and decrease with weight gain (Cummings *et al.*, 2002).

In summary, the presence or absence of food in the GI tract causes the release of a number of peptides that act to optimize the digestive process and regulate appetite and energy expenditure. Levels of these hormones are influenced by meal composition, caloric load, body weight, gender, and other factors. This study aimed to determine the effect of fiber intake on circulating gut hormone levels in humans.

2. Methods

PubMed/Medline was used to identify original research and review articles on September 27, 2010. The following key words and search terms were used: (dietary fiber OR fiber OR fibre OR whole grain OR complex carbohydrate) AND (gut hormones OR ghrelin OR peptide YY OR peptide tyrosine tyrosine OR PYY OR glucagon-like peptide-1 OR glucagon like peptide OR GLP OR GLP-1 OR cholecystokinin OR CCK). All searches were limited to human studies, English language, and peer-reviewed publications. References from original research and review articles were scanned to identify other potentially relevant studies. The following inclusion criteria were used: Adults (19+ years); healthy individuals of any body weight; clinical trials; measurable fiber level and type; outcome data for PYY, GLP-1, CCK, or ghrelin; attrition rates $\leq 20\%$; and studies completed between 1990 and the present. Exclusion criteria included infants; children; people < 19 years of age; people with diabetes, hyperlipidemia, hypertension, hypercholesterolemia, or any other health disorders. Studies that used descriptive (retrospective or prospective) study design only, or studies without a measurable fiber intervention were excluded, as were studies with an attrition rate $> 20\%$. Studies that met the inclusion criteria were further examined for relevance, validity, and quality by evaluating sample population and size, study design (crossover vs. parallel), randomization, blinding, choice of control, and appropriateness of statistical analyses. These characteristics were organized into tables. Studies that lacked a control were excluded at this level of evaluation.

3. Results

3.1 Effect of fiber on peptide YY concentrations

The PubMed search generated a list of 27 publications, including 22 original research articles and 5 review articles (Figure 1). Eleven primary research articles were relevant to the research question, of which 9 were obtained from the PubMed search and 2 were discovered by examining the reference lists from the review articles. Nine of the 11 relevant publications met the quality criteria and were included in the final analysis. More than 11 types of fibers were studied and doses ranged from 3.8 to 27 g. Fiber was primarily supplied via a supplemented grain product (e.g. bread, muffins, or cereal) which was consumed alone or as part of a mixed meal. Alternatively, fiber was provided as a powder added to a beverage. General study characteristics and outcomes are summarized in Table 1.

Three studies examined the effects of β -glucan fibers on PYY response. Two studies used randomized, crossover designs and controls matched for calories and macronutrients. The first measured 3 g barley β -glucan in 14 normal weight volunteers (Vitaglione, Lumaga, Stanzione, Scalfi & Fogliano, 2009). Area under the curve (AUC) measured over 3 hours was significantly higher following β -glucan intake compared to control. In a similar study, 3 doses (2.2-5.5 g) of oat β -glucan were tested in 14 overweight men and women (Beck, Tapsell, Batterham, Tosh & Huang, 2009). PYY levels were compared to control at individual time points (AUC was not compared). The highest dose of β -glucan resulted in significantly higher PYY levels after 4 hours compared to control. A dose response effect was observed for increasing levels of β -glucan. Although these studies are limited by small sample size, they suggest a dose of 3-6 g β -glucan may raise postprandial PYY levels.

One study examined the effects of chronic β -glucan supplementation on PYY levels. In a parallel design, overweight women (n=66) consumed a low calorie diet supplemented with 0, 5-6 or 8-9 g β -glucan for 3 months (Beck, Tapsell, Batterham, Tosh & Huang, 2010). Total fasting PYY decreased in all groups compared to baseline, but the decrease was significantly less for the high dose compared to control. However, it is not possible to distinguish the effects of fiber supplementation from the effects of caloric restriction and weight loss on gut hormone levels.

Two randomized, crossover studies examined the effect of wheat and/or oat fiber on PYY response. Juvonen *et al.* tested 10 g wheat or oat bran alone, 5 g of each in combination, and a control and found no differences in PYY response among treatments (Juvonen *et al.*, 2010). Similarly, Weickert *et al.* tested 10.5 g of added wheat or oat fiber in 14 women and found that postprandial PYY AUC0-300 was blunted following wheat fiber, while PYY levels after oat fiber did not differ from control (Weickert *et al.*, 2006).

Other fiber sources were tested in single studies, but at varying doses. In a randomized, crossover design, subjects (n=20) consumed 0, 4, 8, or 12 g of a mixed fiber (pectin, barley β -glucan, guar gum, pea fiber, and citrus fiber) (Willis *et al.*, 2010). PYY3-36 AUC0-60 did not differ among treatments; however, many samples fell below the assay detection level. In another randomized crossover study, subjects (n=16) consumed 4 isoenergetic meals with varying amounts of psyllium (6.2-27 g) and soy protein or a bread control (Karhunen *et al.*, 2010). The high fiber meals caused a longer elevation of PYY levels compared to control, but this was only significant at 90 min and 120 minutes after the meal; AUC0-120 did not differ.

Two studies using parallel designs examined chronic consumption of a fiber source. Subjects (n=10) consumed 16 g/d of an inulin/oligofructose blend or control for 2 weeks, at which point postprandial PYY was measured in response to a free choice buffet breakfast (Cani *et al.*, 2009). Mean total PYY levels were compared at individual time points (AUC was not measured). Plasma PYY was significantly increased 10 minutes after breakfast in subjects who had been consuming the inulin treatment compared to control. Another study examined the effect of increasing doses (5 to 10 g) of a functional fiber blend consumed for 3 weeks (Reimer *et al.*, 2010). Following intervention, fasting PYY was significantly higher in the supplemented group compared to control, but only in a subset of individuals with BMI <23. In addition, PYY levels at week 3 were not different from baseline.

Overall, the available evidence does not show a clear effect of fiber on PYY levels. Acute feeding studies reported that small amounts of β -glucan or large amounts of psyllium increased postprandial PYY, while wheat and oat brans and a mixed fiber blend did not increase PYY compared to control meals. Chronic, daily consumption of β -glucan combined with energy restriction was shown to decrease fasting levels of PYY, while a mix of inulin and oligofructose or a functional fiber blend had little effect on fasting PYY levels. In general, the available studies are limited by sample size and study design. The wide variety of fiber types and doses used make it difficult to discern an overall relationship between fiber and PYY response.

3.2 Effect of fiber on glucagon-like peptide-1 concentrations

The PubMed search generated a list of 53 publications, including 37 original research articles and 16 review articles, meta-analyses, or letters to the editor (Figure 1). Nineteen primary research articles were relevant to the research question, of which 17 were obtained from the PubMed search and 2 were discovered by examining the reference lists from the review articles. Of the 19 relevant publications, 16 met the quality criteria and were included in the final analysis. Many types of fiber were evaluated, with doses ranging from 1.7 g to 29 g fiber. In 11 studies, the fiber was provided as a supplemented grain product (most commonly bread), while in the other 5 studies, a powdered fiber supplement was mixed with a beverage or other test product. General study characteristics and outcomes are summarized in Table 2.

Several studies tested multiple types and amount of fiber, but only one combination showed a positive impact on GLP-1 levels. In a randomized, crossover design, subjects ($n=15$) consumed 7 test meals with varying levels (9.9-81 g) of dietary fiber plus resistant starch (RS) from various forms of barley, oats, and modified corn starch or a low fiber control (Nilsson, Ostman, Holst & Bjorck, 2008). Test meals were consumed in the evening, and GLP-1 was measured the next morning following a standard breakfast. The total GLP-1 AUC0-120 was significantly higher than control following consumption of the test meal containing 20.2 g fiber + RS from ordinary barley. There were no other differences among treatments. This suggests the source of fiber may be more important than the dose, since other treatments with similar amounts of fiber + RS had no effect. Another study that compared 5.5 g whole wheat barley to control found no differences in GLP-1 AUC0-300 following the test meal (Najjar *et al.*, 2009).

Additional studies have evaluated the effect of fiber from other whole grain sources on GLP-1 response. Two crossover studies compared various types and doses (6.1-29 g) of rye bread to a low-fiber white bread matched for available carbohydrates. In both studies, GLP-1 AUC0-180 did not differ among treatments (Juntunen *et al.*, 2002; Juntunen, Laaksonen, Poutanen, Niskanen & Mykkanen, 2003). A high fiber rye bread (whole meal rye bread enriched with rye bran) providing 29 g fiber caused significantly greater GLP-1 values compared to control at 150 and 180 minutes postprandially (Juntunen *et al.*, 2003). However, this product was also higher in energy, fat, and protein, so it is unclear if fiber was responsible for the observed effects. A rye bread enriched with β -glucan (17.1 g fiber, including 5.4 g β -glucan) also increased GLP-1 compared to control later in the postprandial period (120 and 150 minutes) (Juntunen *et al.*, 2002). In a randomized, crossover design, Weickert *et al.* examined the effect of 10.5 g wheat or oat fiber compared to control and found no differences among treatments in GLP-1 measured as AUC0-300 or individual time points (Weickert *et al.*, 2005). Similarly, ancient wheat Einkorn (4-6 g) did not alter GLP-1 AUC0-180 compared to a modern wheat bread (Bakhoj, Flint, Holst & Tetens, 2003). However, fiber differences between control and treatment were minor and the sample size was small ($n=11$).

Psyllium was tested in two randomized, crossover trials. In the first, subjects ($n=10$) consumed a meal with added psyllium (1.7 g) and/or fat or an unsupplemented meal matched for available carbohydrates (Frost, Brynes, Dhillon, Bloom & McBurney, 2003). GLP-1 AUC0-240 was significantly higher than control in the meal with added psyllium and fat, but this effect was likely due to caloric differences between meals. AUC was not different between control and the low fat psyllium treatment, which was matched for calories (Frost *et al.*, 2003). In a later study, isoenergetic meals with varying levels of psyllium (6.2-27 g) and protein were compared to an unsupplemented control (Karhunen *et al.*, 2010). GLP-1 AUC0-120 did not differ among treatments, but GLP-1 concentrations decreased below baseline following consumption of the high fiber, high protein treatment, indicating a negative effect of fiber and/or protein on GLP-1 levels.

Two studies tested pea fiber, either alone or as part of a mixed fiber blend. In a study by Raben *et al.*, subjects ($n=10$), consumed a meal supplemented with 25.5 g pea fiber or low fiber control matched for energy and macronutrients (Raben, Christensen, Madsen, Holst & Astrup, 1994). There were no differences in GLP-1 between treatments when measured as AUC0-240 or at individual time points. Willis *et al.* examined the effect of muffins supplemented with 0, 4, 8, or 12 g of a mixed fiber (pectin, barley β -glucan, guar gum, pea fiber, and citrus fiber) and found that GLP-1 AUC0-60 was significantly higher for the 0 g dose than the 4 and 12 g doses, which again suggests a potential suppressive effect of fiber on GLP-1 (Willis *et al.*, 2010).

Three randomized, crossover trials measured GLP-1 response to fiber dissolved in a test beverage. Two studied the effect of a preload of guar gum (2.5 g) + galactose or water (control), followed by a test meal (Adam & Westerterp-Plantenga, 2005a; Adam & Westerterp-Plantenga, 2005b). In both studies, GLP-1 levels were increased compared to control between 30 and 60 minutes postprandially. However, this is not a useful comparison since GLP-1 is known to increase as a result of caloric load. The fiber treatment contained 200 kcal

and was compared to a non-caloric control. In another study, there were no differences in GLP-1 AUC0-360 between a beverage containing 24 g inulin + 56 g high fructose corn syrup (HFCS) and beverages with 80 g or 56 g of HFCS alone (Tarini & Wolever, 2010).

Three studies with parallel design have evaluated the effect of chronic fiber supplementation on GLP-1 levels. Consumption of oat β -glucan (5-6 or 8-9 g/d) as part of a reduced calorie diet led to a reduction in fasting GLP-1 levels after 3 months (Beck *et al.*, 2010). Values were not different from a control group on the same low calorie diet, suggesting that weight loss has a greater effect on gut hormone levels than fiber. In another study, subjects consumed increasing doses (5 to 10 g) of a novel functional fiber or control for 3 weeks (Reimer *et al.*, 2010). There were no differences in fasting GLP-1 levels at the end of the treatment period. Similarly, fasting GLP-1 levels were not different in subjects receiving 16 g/d of an inulin/oligofructose blend or control for 2 weeks (Cani *et al.*, 2009). However, GLP-1 was elevated compared to control at 10 minutes following a standard meal in subjects who had consumed fiber; AUC was not evaluated. These studies suggest chronic fiber intake independent of weight changes does not impact GLP-1 levels. In addition, due to the parallel design, these studies must be interpreted with caution, given the inter-individual variability in gut hormone levels.

The available research suggests that fiber does not increase GLP-1 levels compared to control. Most studies were limited by sample size or design. Only one study reported an increase in GLP-1 AUC following fiber intervention (20.2 g ordinary barley), and other studies with similar types or doses of fiber found no effect. High doses of fiber (17-29 g) from rye bread significantly increased GLP-1 between 2 and 3 hours after a test meal, but at no other time points. Other fiber interventions showed no effect on GLP-1 concentrations when matched for calorie content.

3.3 Effect of fiber on cholecystokinin concentrations

The PubMed search generated a list of 64 publications, including 47 original research articles and 17 review articles, meta-analyses, or letters to the editor (Figure 1). No additional articles were discovered from examination of review article reference lists. Eleven primary research articles were relevant to the research question, of which 9 met the quality criteria and were included in the final analysis. Fiber came from a variety of sources, but β -glucan sources were the most common; fiber doses ranged from 3.7 to 35.5 g fiber. While most studies provided fiber as part of a mixed meal, one used a fiber-supplemented liquid formula. Control meals were generally well matched to the treatment meals in terms of energy and macronutrients. General study characteristics and outcomes are summarized in Table 3.

Several studies evaluated CCK response to supplementation with fibers containing β -glucans. Test cereals containing varying amounts of oat β -glucan (2.16-5.65 g) were compared to a low fiber cereal in a randomized, crossover design (Beck *et al.*, 2009). There was a significant dose response for women ($n=7$), but the combined sex analyses showed no differences in CCK AUC0-240. A similar gender effect was observed in subjects consuming mixed meals containing 7 g (control) or 20 g fiber (added fiber in the high fiber meal was primarily from oats) (B. Burton-Freeman, Davis & Schneeman, 2002). In women, the high fiber meal elicited a significantly higher mean CCK response compared to control, while the CCK response between meals did not differ in men. In another study, male volunteers ($n=11$) consumed pasta made from barley with high β -glucan content (15.7 g fiber; 5 g β -glucan) or control (Bourdon *et al.*, 1999). CCK AUC0-360 did not differ, but the pattern of CCK response was different. While CCK concentrations returned to baseline by 3 hours after the low fiber meal, CCK levels did not return to baseline until 6 hours following the high fiber meal.

In a chronic study using a parallel design, consumption of oat β -glucan (5-6 or 8-9 g/d) as part of a reduced calorie diet for 3 months did not alter fasting CCK levels compared to control in women (Beck *et al.*, 2010). Another chronic study evaluated addition of 20 g partially hydrolyzed guar gum (PHGG) to a very low calorie formula diet in obese women ($n=25$) (Heini *et al.*, 1998). Women received PHGG during either week 3 or 5 of the diet. Following a meal challenge using the formula diet, average CCK concentrations did not differ between treatment and control.

Additional randomized, crossover trials have evaluated different types of fiber or types of carbohydrate. In a small study, men ($n=10$) consumed a test meal with 12 g fiber from bean flakes or a low fiber meal matched for energy and macronutrients (Bourdon *et al.*, 2001). The bean flake meal produced almost twice the CCK AUC0-360 response, which was statistically significant. Pasman *et al.* compared the effect of isoenergetic meals containing complex or simple carbohydrates in 26 male volunteers (Pasman, Blokdijk, Bertina, Hopman & Hendriks, 2003). The complex carbohydrate meal contained 6.7 g of fiber, provided primarily by rye bread. There was no difference in CCK response between the meals when measured as AUC0-240 or at individual time points.

Two studies compared meals that differed in glycemic index. The first found that consumption of a low fiber (2.4 g), high glycemic index meal resulted in a significantly greater CCK AUC0-480 compared to a high fiber (35.5 g), low glycemic index meal in female volunteers (n=22) (B. M. Burton-Freeman & Keim, 2008). In contrast, when matched for fiber content (29-30 g), consumption of a low glycemic index meal resulted in significantly greater CCK AUC0-420 in men (n=12) (Reynolds, Stockmann, Atkinson, Denyer, & Brand-Miller, 2009).

The available evidence indicates that fiber does not have a consistent effect on CCK levels. In a small, but well designed study, fiber from bean flakes caused a clear increase in CCK compared to control, but the results are applicable only to men. Acute consumption of fiber from oats may increase CCK in women only, while chronic intake of fiber has no effect. In addition, meals varying in type of carbohydrate yielded inconsistent effects on CCK. Most studies were limited by small sample size, and may not be representative of the general population since they were conducted in certain genders, BMI ranges, or individuals on a reduced calorie diet.

3.4 Effect of fiber on ghrelin concentrations

The PubMed search generated a list of 51 publications, including 40 original research articles and 11 review articles, meta-analyses, or letters to the editor (Figure 1). Twenty-three primary research articles were relevant to the research question, of which 19 were obtained from the PubMed search and 4 were discovered by examining the reference lists from the review articles. Of the 23 relevant publications, 19 met the quality criteria and were included in the final analysis. A variety of individual fibers and fiber blends were studied, with doses ranging from 2 to 52 g fiber. Twelve studies provided fiber as a supplemented grain product or as part of a mixed meal, 5 added powdered fiber to a liquid or semi-solid product, and 2 added fiber to water. General study characteristics and outcomes are summarized in Table 4.

Several studies measured ghrelin response to β -glucan supplementation. In a randomized, crossover design, subjects (n=14) consumed isoenergetic breads enriched with 3 g barley β -glucan or control (Vitaglione *et al.*, 2009). Ghrelin AUC60-180 was significantly lower following the fiber treatment. In contrast, there were no differences in ghrelin AUC0-240 among subjects (n=14) consuming cereal supplemented with varying doses of oat β -glucan (2.16-5.65 g) or control matched for available carbohydrate and protein (Beck *et al.*, 2009). Similarly, in a 3 month parallel trial, supplementation with oat β -glucan (5-6 or 8-9 g) had no effect on fasting ghrelin levels in women on a reduced calorie diet (Beck *et al.*, 2010). However, it possible that any effect of fiber would have been overshadowed by the influence of weight change on gut hormone levels. Additional randomized, crossover trials using 10-10.5 g fiber from oats or wheat did not show a suppressive effect of fiber on ghrelin levels compared to an isoenergetic control (Juvonen *et al.*, 2010; Weickert *et al.*, 2006). In fact, one study found that 10.5 g wheat fiber resulted in significantly higher ghrelin AUC0-180 compared to control (Weickert *et al.*, 2006).

A series of crossover studies examined the effects of carob fiber on postprandial ghrelin levels. In the first study, subjects (n=20) consumed a liquid meal alone or enriched with 5, 10, or 20 g carob fiber (Gruendel *et al.*, 2006). Acylated (but not total) ghrelin was significantly lower 60 minutes after the test meal for all doses of fiber compared to control. There were no other differences over the 5 hour postprandial period, and AUC was not analyzed. In contrast, the same doses of carob fiber added to glucose water had no effect on acylated ghrelin, but the 10 g dose decreased total ghrelin compared to control (Gruendel, Otto *et al.*, 2007). In a third study, volunteers consumed calorie and nutrient matched meals with or without 50 g carob fiber, followed by an overnight fast (Gruendel *et al.*, 2007). Ghrelin was measured the next morning following ingestion of a standardized white bread. Fasting acylated (but not total) ghrelin was significantly higher following consumption of the meal enriched with carob fiber; there were no differences in postprandial ghrelin levels.

There were 9 additional acute, crossover studies with fiber and ghrelin, each testing different types of fiber. In a study by Karhunen *et al.*, subjects (n=16) consumed isoenergetic meals with varying levels of psyllium (7.6-27 g) and protein or a low fiber, low protein control in randomized order (Karhunen *et al.*, 2010). The declines in total ghrelin, measured as AUC0-120 after the high fiber meals were blunted and differed significantly from the low fiber meals. Similarly, in subjects (n=11) consuming a meal with 6 g arabinoxylan or control matched for energy and macronutrients, ghrelin suppression was greater following control (Mohlig *et al.*, 2005). In a study by Willis *et al.*, subjects (n=20) consumed muffins with 0, 4, 8, or 12 g of a mixed fiber in random order (Willis *et al.*, 2010). There were no differences in AUC0-90 between treatments and control, but the highest dose led to significantly higher values than the lower doses. Consumption of rye products with varying levels of fiber (6.5-12.3 g) did not alter ghrelin AUC0-180 compared to low fiber control matched for available carbohydrates

(Rosen *et al.*, 2009). These studies suggest that fiber does not have a suppressive effect on ghrelin, and that certain fibers may actually blunt the decline in postprandial ghrelin levels.

In contrast, several studies have reported greater declines in ghrelin levels following fiber compared to control. Consumption of bread enriched with lupin kernel flour (15 g fiber) resulted in significantly lower plasma ghrelin values than a calorie-matched white bread over a 3 hour postprandial period (Lee *et al.*, 2006). However, the enriched bread also contained twice the protein as control, so it is unclear if the effects are due to fiber, protein, or the combination. Consumption of 6 g fiber from plums produced significantly lower ghrelin values compared to white bread, but only at 15 and 30 minutes after the meal; there were no differences in ghrelin AUC₀₋₁₂₀ (Furchner-Evanson, Petrisko, Howarth, Nemoseck & Kern, 2010). Addition of 24 g inulin to a HFCS beverage caused a significant decrease in ghrelin levels compared to control, but not until 4 hours later, after a standard test lunch was consumed (Tarini & Wolever, 2010). This suggests that fiber may produce a 2nd meal effect on ghrelin levels. Although these studies suggest a suppressive effect of fiber on ghrelin, any effects appear to be short lived.

Two studies tested the influence of different types of carbohydrate on ghrelin levels. Ghrelin response was not different when subjects consumed a high glycemic index meal or a low glycemic index meal with similar fiber content (Reynolds *et al.*, 2009). In another study, subjects consumed meals containing simple or complex carbohydrates at varying calorie levels, but with similar fiber content (Blom *et al.*, 2005). The decrease in ghrelin AUC₀₋₂₄₀ was greater for the high calorie, simple carbohydrate meal than for the high calorie, complex carbohydrate meal, which suggests carbohydrate structure may affect ghrelin levels, regardless of fiber content.

Two additional studies examined the effect of chronic fiber supplementation on fasting ghrelin levels. In a randomized, crossover design, subjects consumed 12 g/d pullulan, RS, soluble fiber dextrin, soluble corn fiber or control for 2 weeks each. There were no differences in fasting ghrelin among treatments (Stewart, Nikhanj, Timm, Thomas & Slavin, 2010). Similarly, consumption of a novel functional fiber for 3 weeks did not alter fasting ghrelin levels compared to a control diet (Reimer *et al.*, 2010). However, this study was limited by parallel design.

The available evidence suggests fiber does not positively influence postprandial ghrelin levels. The majority of studies found that fiber had no effect or a negative effect on ghrelin (higher levels compared to control) over a range of fiber sources and doses. In the few studies showing a suppressive effect of fiber, lower ghrelin values were only observed at limited time points throughout the postprandial period. However, many of these studies were limited by small sample size, lack of crossover design, or use of a control that differed in variables other than fiber content.

4. Discussion

The available literature on fiber and gut hormones is limited in both quality and quantity. Few studies with strong design (randomized, controlled, double-blind, crossover trials) measure gut hormone levels following acute fiber intake. Therefore, to provide a more complete assessment of the literature, studies with parallel design and those that measured fasting hormone levels after chronic fiber intake were also included in this review. Gut hormone levels can be highly variable from individual to individual, so the reliability of results from those studies is unknown. There is also little consistency in the types of fibers and doses used across studies, and a wide variety of isolated fibers, synthetic fibers, and high-fiber whole foods were used. Furthermore, control treatments differed greatly among studies and were not always appropriate for examining the effect of fiber supplementation. Since the primary outcome was gut hormone levels compared to control, the use of inappropriate control treatments could significantly alter the results. These variations make it difficult to discern the true effect of fiber on gut hormone levels.

Few studies have been conducted investigating the effect of fiber on PYY release. Only nine publications met the inclusion criteria for the current review, resulting in 20 fiber-control comparisons based on many different fiber types and levels. Of those comparisons, the influence of fiber on circulating PYY levels was seen with acute feeding of test meals containing 3-6 g barley or oat β -glucan or greater than 25 g psyllium. Generally, fat and protein, as well as calorie load of a meal, have a greater influence on release of PYY into circulation than carbohydrates (Batterham *et al.*, 2006; Essah *et al.*, 2007; MacIntosh *et al.*, 1999). Fiber, as a member of the carbohydrate family of macronutrients, might not be expected to influence PYY to a great extent beyond the provision of calories to a meal.

Sixteen publications investigating the effect of fiber on GLP-1 release met the inclusion criteria for the current review, resulting in 34 fiber-control comparisons based on many different fiber types and levels. Of those comparisons, influence of fiber meals on circulating GLP-1 levels were seen primarily when differences in

calorie content of the products were reported. For instance, in a study of psyllium, an increase in circulating GLP-1 was found when fat, and therefore calories, was added to the test meal, but not when the meals were matched for energy (Frost *et al.*, 2003). Circulating GLP-1 levels are known to be influenced by calories consumed, however when calorie content of a meal is held constant, carbohydrates and proteins are potent stimulators of GLP-1 release (Bowen *et al.*, 2006; Raben *et al.*, 2003). The results of this review suggest that calories are a more potent stimulator of GLP-1 release into the bloodstream than fiber. Any effect of fiber on appetite through GLP-1 action may be mediated directly via the vagal nerve and not as a result of circulating GLP-1.

Nine publications investigating the effect of fiber on circulating levels of CCK met the inclusion criteria for the current review, resulting in only 14 fiber-control comparisons based on many different fiber types and levels. In general, the results would suggest that fibers are not efficacious in promoting higher levels of circulating CCK. These results should not be surprising as carbohydrates have not been found to be as robust in their influence on circulating CCK levels as either protein or fat. Based on this review, two areas of interest for further investigation are the influence of beans and glycemia on CCK release (Bourdon *et al.*, 2001; Reynolds *et al.*, 2009). Although only 1 study has been published examining bean flakes, the results were quite promising with twice the response, based on AUC, when compared to a control meal. The efficacious component of the bean may be the protein and/or phytonutrient co-passengers in the formulation. Glycemic index of a meal was examined by Reynolds and coworkers (2009) with a report that, when controlled for fiber content of the meal, glycemic index significantly influenced the CCK response to the meal (Reynolds *et al.*, 2009). Preliminary research has suggested that glycemia may influence appetite and satiety and this is the first report that suggests that one mechanism may be related to CCK release. More research is needed in both of these areas to confirm these early findings.

Ghrelin is known to be influenced by consumption of food. The increase in ghrelin levels between meals is generally reversed once food is consumed. Some data suggest that protein and carbohydrates are more effective than lipids at attenuating the rise in ghrelin, however the presence of food in the gut may be the primary precipitating factor. Nineteen publications investigating the effect of fiber on attenuating the rise in circulating levels of ghrelin met the inclusion criteria for the current review, resulting in 44 fiber-control comparisons. Although several studies examining specific time points following the meal suggest that the influence of fiber on ghrelin may be time-specific, other data suggest that inclusion of fiber in a meal may actually blunt the postprandial decrease in ghrelin. In general, data reported as AUC did not support the hypothesis that fiber suppresses ghrelin levels.

Other issues complicating gut hormone research are related to the technological aspects and limitations involved in the measurement of gut hormones. Most studies rely on more affordable, but less sophisticated techniques, such as enzyme immunoassay or radio immunoassay, for gut hormone analysis (Delzenne *et al.*, 2010). These often measure the total amount of the peptide, rather than a specific form. In many cases, only certain forms of a hormone may be bioactive, so measuring the total concentration may not be entirely informative. In addition, some studies have shown changes in one form of a peptide, but not another (e.g. acylated ghrelin vs. total ghrelin), suggesting that measuring total peptide amounts is providing an incomplete picture (Gruendel *et al.*, 2006). Furthermore, degradation of some peptides (e.g. GLP-1 by DPP-IV) both in the blood and in stored samples could lead to inaccurate measurements and interpretations. In addition, since many gut hormones bind their receptors and exert actions in the gut, measurement of these peptides in venous blood may not be meaningful in terms of their physiological effects.

The primary reason for measuring gut hormones following fiber intervention is to identify potential mechanisms by which fiber may influence appetite. However, it is important to consider the fact that individual gut hormones are not released in isolation following a meal. Instead, they are released in concert with other hormones and peptides which act together to control the digestion and absorption process and signal energy needs. Nevertheless, most studies focus on individual hormones as independent contributors to the primary outcome of appetite. Specific combinations of gut hormones have been shown to have additive effects on outcomes such as inhibition of food intake, and other synergistic relationships may exist (Neary *et al.*, 2005). By studying each hormone in isolation, we may be missing the bigger picture.

The available research does not support a consistent effect of fiber on modifying circulating gut hormone levels. While it is possible that fiber does not influence appetite via gut hormone pathways, it is also possible that the lack of consistent study design merely prevents us from forming conclusions around this relationship. Current research uses a wide variety of fiber sources with different physical and chemical properties which may influence gut hormone response. Different fiber types may influence gut hormone levels based on their

physicochemical properties, but additional research is required to examine this relationship. The relationship between fiber intake and appetite may also work by mechanisms not detectable with the measurement of circulating gut hormone levels.

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Table 1. Studies measuring effect of fiber on PYY

Ref	N	X/P	C/A	Fiber Type	Fiber Dose	PYY Increase vs. Control
Vitaglione 2009	14	X	A	barley concentrate	β -glucan 3 g	Yes
Beck 2009	14	X	A	oat β -glucan	2.2 g	No
				oat β -glucan	3.8 g	No
				oat β -glucan	5.5 g	Yes (2-4 h after test meal)
Beck 2010	66	P	C	β -glucan	5-6 g/d x 3 months	No (fasting values)
				β -glucan	8-9 g/d x 3 months	No (fasting values)
Juvonen 2010	20	X	A	wheat bran	10 g	No
				oat bran	10 g	No
				wheat bran + oat bran	5 g each	No
Weickert 2006	14	X	A	wheat fiber	10.5 g	No
				oat fiber	10.6 g	No
Willis 2010	20	X	A	mixed fiber	4 g	No
				mixed fiber	8 g	No
				mixed fiber	12 g	No
Karhunen 2010	16	X	A	psyllium + low protein	7.6 g	No
				psyllium + low protein	27 g	Yes
				psyllium + high protein	6.2 g	No
				psyllium + high protein	25.8	Yes
Cani 2009	10	X	C/A	inulin/oligofructose blend	16 g x 2 wks	Yes (but only at 10 min after standardized non-fiber meal on day 14)
Reimer 2010	54	P	C	Functional fiber blend	5 g/d x 1 wk, then 10 g/d x 2 wks	Yes (in BMI <23; values not different from baseline)

A, acute intake; C, chronic intake; C/A, chronic intake, acute meal challenge; P, parallel design; X, crossover design

Table 2. Studies measuring effects of fiber on GLP-1

Ref	N	X/P	A/C	Fiber Type	Fiber Dose	GLP-1 Increase vs. Control
Beck 2010	66	P	C	β -glucan	5-6 g/d x 3 months	No (fasting values)
				β -glucan	8-9 g/d x 3 months	No (fasting values)
Willis 2010	20	X	A	mixed fiber	4 g	No
				mixed fiber	8 g	No
				mixed fiber	12 g	No
Karhunen 2010	16	X	A	psyllium + low protein	7.6 g	No
				psyllium + low protein	27 g	No
				psyllium + high protein	6.2 g	No
				psyllium + high protein	25.8	No
Cani 2009	10	X	C/A	inulin/oligofructose blend	16 g x 2 wks	Yes (but only at 10 min after standardized non-fiber meal on day 14)
Reimer 2010	54	P	C	functional fiber blend	5 g/d x 1 wk, then 10 g/d x 2 wks	No (fasting values)
Nilsson 2008	15	X	A	ordinary barley	20.2 g	Yes
				cut ordinary barley	19.4 g	No
				ordinary barley	9.9 g	No
				high amylose barley	38.1 g	No
				high b-glucan barley	81 g	No
				resistant starch	11.5	No
Najjar 2009	10	X	A	whole wheat bread	6.3 g	Yes
				whole wheat barley bread	5.5 g	No
Juntunen 2002	20	X	A	whole kernel rye	12.8 g	No
				whole meal rye with oat b-glucan concentrate	17.1 g	Yes (but only at 120 and 150 min after meal)
				dark durum wheat pasta	5.6 g	No
Juntunen 2003	19	X	A	endosperm rye	6.1 g	No
				whole-meal rye	15.2 g	No
				whole-meal rye enriched with rye bran	29 g	Yes (but only at 150 and 180 min after meal)
Weickert 2005	14	X	A	wheat fiber	10.5 g	No
				oat fiber	10.6 g	No
Bakhoj 2003	11	X	A	ancient wheat Einkorn	4-6 g	No
Frost 2003	10	X	A	psyllium	1.7 g	No
				psyllium + fat	1.7g	Yes
Raben 1994	10	X	A	pea fiber	25.5 g	No
Adam 2005a	58	X	A	guar gum (+galactose)	2.5 g	Yes (but vs. water; important kcal difference)
Adam 2005b	30	X	A	guar gum (+galactose)	2.5 g	Yes (but vs. water; important kcal difference)
Tarini 2010	12	X	A	inulin (+HFCS)	24 g	No

A, acute intake; C, chronic intake; C/A, chronic intake, acute meal challenge; HFCS, high fructose corn syrup; P, parallel design; X, crossover design

Table 3. Studies measuring effect of fiber on CCK

Ref	N	X/P	C/A	Fiber Type	Fiber Dose	CCK Increase vs. Control
Beck 2009	14	X	A	β -glucan	2.16 g	No
				β -glucan	3.82 g	No
				β -glucan	5.45 g	No
				β -glucan + oat	5.65 g	No
				β -glucan concentrate		(Dose response in women)
Beck 2010	66	P	C	β -glucan	5-6 g/d x 3 months	No (fasting values)
				β -glucan	8-9 g/d x 3 months	No (fasting values)
Burton-Freeman 2008	16	X	A	oat bran	20 g	Yes (women only)
Bourdon 1999	11	X	A	β -glucan enriched fraction of barley flour	15.7 g, including 5g β -glucan	No (elevated above baseline for 6 hrs vs. 3 hrs in ctl.)
				barley flour naturally high in β -glucan	15.7 g, including 5g β -glucan	No
Heini 1998	25	X	C	partially hydrolyzed guar gum	20 g	No
Bourdon 2001	10	X	A	bean flakes	12 g	Yes
Pasman 2003	26	X	A	complex carbohydrate	6.7 g	No (vs. low fiber, simple carbohydrate meal)
Burton-Freeman 2008	22	X	A	low glycemic index meal	35.5 g	No
Reynolds 2009	12	X	A	low glycemic index meal	30 g	Yes (vs. high glycemic meal with equal fiber)

A, acute intake; C, chronic intake; C/A, chronic intake, acute meal challenge; P, parallel design; X, crossover design

Table 4. Studies examining effects of fiber on ghrelin

Ref	N	X/P	C/A	Fiber Type	Fiber Dose	Ghrelin Decrease vs. Control
Vitaglione 2009	14	X	A	barley β -glucan concentrate	3 g	Yes (AUC60-180)
Beck 2009	14	X	A	β -glucan	2.16 g	No
				β -glucan	3.82 g	No
				β -glucan	5.45 g	No
				β -glucan + oat β -glucan	5.65 g	No
Beck 2010	66	P	C	β -glucan	5-6 g/d x 3 months	No (fasting values)
				β -glucan	8-9 g/d x 3 months	No (fasting values)
Juvonen 2010	20	X	A	wheat bran	10 g	No
				oat bran	10 g	No
				wheat bran + oat bran	5 g each	No
Weickert 2006	14	X	A	wheat fiber	10.5 g	No
				oat fiber	10.6 g	No
Willis 2010	20	X	A	mixed fiber	4 g	No
				mixed fiber	8 g	No
				mixed fiber	12 g	No
Karhunen 2010	16	X	A	psyllium + low protein	7.6 g	No
				psyllium + low protein	27 g	No
				psyllium + high protein	6.2 g	No
				psyllium + high protein	25.8	No
Reimer 2010	54	P	C	functional fiber blend	5 g/d x 1 wk, then 10 g/d x 2 wks	No
Tarini 2010	12	X	A	inulin (+HFCS)	24 g	Yes (after a lunch 4-6 hours after the test meal)
Reynolds 2009	12	X	A	low glycemic index meal	30 g	No
Gruendel 2006	20	X	A	carob fiber (in mixed meal)	5 g	Yes (acylated only)
				carob fiber (in mixed meal)	10 g	Yes (acylated only)
				carob fiber (in mixed meal)	20 g	Yes (acylated only)
Gruendel 2007; 98(1)	20	X	A	carob fiber (in glucose water)	5 g	No
				carob fiber (in glucose water)	10 g	No
				carob fiber (in glucose water)	20 g	No
Gruendel 2007; 98(6)	19	X	A	carob fiber	45 g	No
Mohlig 2005	11	X	A	Arabinoxylan	6 g	No
Rosen 2009	12	X	A	Endosperm rye bread	6.7 g	No
				Whole grain rye bread	9.6 g	No
				Rye bran bread	12.3g	No
				Endosperm rye porridge	6.5 g	No
				Whole grain rye porridge	10.1 g	No
Lee 2006	17	X	A	lupin kernel	15 g	Yes
Furchner-Evanson 2010	19	X	A	fiber from dried plums	6 g	Yes (but only at 15 and 30 min after meal)
Blom 2005	20	X	A	low kcal meal (fiber from fruit)	14 g	No
				high kcal, simple carbohydrate	12 g	No
				high kcal, complex carbohydrate	12 g	No
Stewart 2010	20	X	C	pullulan	12 g/d x 2 wks	No (fasting values)
				resistant starch	12 g/d x 2 wks	No (fasting values)
				soluble fiber dextrin	12 g/d x 2 wks	No (fasting values)
				soluble corn fiber	12 g/d x 2 wks	No (fasting values)

A, acute intake; C, chronic intake; C/A, chronic intake, acute meal challenge; HFCS, high fructose corn syrup; P, parallel design; X, crossover design

