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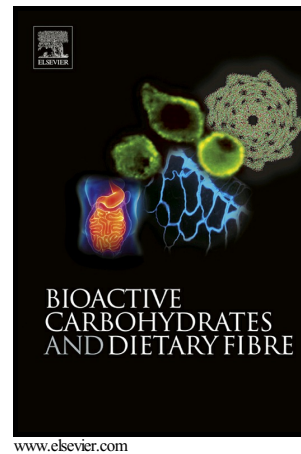
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The impact of dietary fibres on the physiological processes governing small intestinal digestive processes

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Abstract

This review is the second in a series of three articles considering how different types of dietary fibre may affect gut function and health, focusing on the impact of dietary fibre intake on the small intestinal digestive processes. While the small intestinal structure supports the large proportion of gastrointestinal absorption that occurs there, the processes of digestion of macronutrients are largely dependent on the exocrine secretions of the pancreas and liver. The impact of dietary fibre, either as isolates or an integral part of foods such as fruits and vegetables, is therefore also considered on the exocrine functions of these accessory organs.

The physiological processes of these three interconnected organs of digestion are outlined and the evidence that dietary fibre impacts on these processes is considered. Evidence for the association of long-term dietary fibre intake on health outcomes related to these organs is also evaluated.

Keywords [up to 6 keywords]

Introduction

This review is a second of a series of three aimed at pooling together some of the recent evidence that dietary fibre impacts many major aspects of gastrointestinal physiology. The first of these reviews (Brownlee, 2014) focused on the effect of various types of dietary fibre on gastrointestinal processes from the mouth to the stomach. Here, the authors focus on the impact of dietary fibres on the physiology of the small intestine and its accessory organs (the liver and pancreas). Similar to the previous review, this article will consider the impact of a wide range of dietary fibres both as isolates and within fibre-rich foods on the physiological function of this section of the gastrointestinal tract. A subsequent review within this journal will focus on how dietary fibres impact on the physiological processes of the large intestine.

The small intestine is the major site of absorption of the end products of the digestive process due to its enormous surface area (a result of three levels of anatomical folding (Helander & Fändriks, 2014)) and orchestrated motility (WorsØe, Fynne, Gregersen, Schlageter, Christensen, Dahlerup, et al., 2011). To allow macronutrient digestion, the small intestine must also act as a major site of digestion, although this process is almost entirely dependent on exocrine secretions from the pancreas and liver (Chandra & Liddle, 2013; Maldonado-Valderrama, Wilde, Maclerzanka, & MacKie, 2011; Nawrot-Porabka, Jaworek, Leja-Szpak, Kot, & Lange, 2015). These accessory organs are not only important in allowing appropriate intestinal digestion to occur but also in orchestrating the body's utilisation of the products of digestion and possibly linking dietary intake to many longer-term systemic disease trajectories (Strowig, Henao-Mejia, Elinav, & Flavell, 2012; Unger, Clark, Scherer, & Orci, 2010). Although the ideas that dietary fibres can affect the processes of digestion and absorption and can impact on systemic health are not new, the putative mechanisms through which such effects could be brought are often poorly characterised and do not always agree with longer-term studies on health outcomes.

This review therefore aims to explore the potential of dietary fibres to impact short-term changes in small intestinal, pancreatic and hepatic function and to evaluate longer-term impacts on health outcomes related to the correct functioning of these organs in relation to the processes of digestion.

Dietary fibres and the commencement of the intestinal phase of digestion

During the non-digestive state, small intestinal motility is limited to a series of migrating motor complexes which are believed to maintain aboral movement of luminal contents to reduce the build-up of secreted mucus and other secreted factors and to limit the potential of microbial infiltration into the underlying mucosa (Birchenough, Johansson, Gustafsson, Bergström, & Hansson, 2015; Pelaseyed, Bergström, Gustafsson, Ermund, Birchenough, Schütte, et al., 2014). Motility patterns rapidly shift as a result of the pyloric sphincter allowing chyme to enter the duodenum. This action also heralds the commencement of the intestinal phase of digestion. The motility pattern within the intestinal phase of digestion consists of migrating, clustered contractions that tend to move contents along the small intestine up to 30 centimetres at a time at varying frequencies (Otterson, Leming, Fox, & Moulder, 2010; Otterson & Sarr, 1993). Segmentation along the small intestine ensures adequate mixing of luminal contents with digestive juices and improves the chances of contact with the villi (Gwynne, Thomas, Goh, Sjövall, & Bornstein, 2004; Huizinga & Lammers, 2009). The villi themselves pass through the luminal content in waving motions, as a result of the contraction of both the muscularis mucosae as well as the action of the surrounding smooth muscle layers below the mucosa (Schulze, 2015). This smooth muscle in the intestine features distinct, continuous bands

of longitudinal and circular muscle along the entire length of the duodenum, jejunum and ileum (Huizinga & Lammers, 2009). Within the intestinal phase of digestion, a series of reflexes act to control the distal and proximal motility of the gut (Brownlee, 2011). The myenteric reflex, driven by local distension of the gut wall by a bolus of digesta, results in a local increase in the number and strength of contractions mediated by the myenteric plexus within the smooth muscle layers (Fujita, Okishio, Fujinami, Nakagawa, Takeuchi, Takewaki, et al., 2004). The myenteric reflex is initiated by the interstitial cells of Cajal and is driven by release of acetylcholine (Klein, Seidler, Kettenberger, Sibaev, Rohn, Feil, et al., 2013), leading to the orchestration of contraction and relaxation events in the immediate vicinity. Separate neurohumorally-driven feedback mechanisms also occur, as a result of digesta entering the duodenum. This impacts on gastric activity and also leads to a reflex increase in motility of the jejunum, ileum and large intestine (Furness, Rivera, Cho, Bravo, & Callaghan, 2013) to ensure that subsequent segments of the gut are prepared to receive the incoming luminal content.

As acidic digesta (chyme) enters the duodenum from the stomach, this triggers perhaps the key event in the commencement of the intestinal phase of digestion. Cholecystokinin (CCK) is released from the enteroendocrine I cells in the duodenum, resulting in an increase in pancreatic secretion (Y. U. Wang, Prpic, Green, Reeve Jr, & Liddle, 2002) and release of bile from the gall bladder (West & Mercer, 2004). Alongside secretin, motilin and gastric inhibitory peptide, CCK release appears to orchestrate the small intestinal digestive processes and may also have roles in the reduction of gastric secretion and increased intestinal motility (Ellis, Chambers, Gwynne, & Bornstein, 2013; West & Mercer, 2004). Previous studies note that the presence of luminal amino acids is key to CCK release (Daly, Al-Rammahi, Moran, Marcello, Ninomiya, & Shirazi-Beechey, 2013). The presence of low concentrations of amino acids in chyme, as a result of protein digestion in the stomach, is possible but may also be dependent on the presence of basal protease activity in the intestine (Nishi, Hara, Hira, & Tomita, 2001).

Studies in animals and humans have noted that some types of dietary fibre appear to impact on circulating concentrations of CCK. Human studies have particularly focused on the acute, postprandial impact of fibre ingestion on plasma CCK levels. Purified preparations of cellulose and hydrolysed guar gum were shown to significantly increase the amplitude and time length of postprandial CCK peaks (Geleva, Thomas, Gannon, & Keenan, 2003; Heini, Lara-Castro, Schneider, Kirk, Considine, & Weinsier, 1998), while flaxseed fibre and polydextrose appeared to have no effect (Kristensen, Savorani, Christensen, Engelsen, Bügel, Toubro, et al., 2013; Olli, Salli, Alhoniemi, Saarinen, Ibarra, Vasankari, et al., 2015). A similar increase in postprandial CCK response was noted upon inclusion of dried bean flakes (which increased dietary fibre content by almost 12 g/100 g) in a test meal compared to the bean-free control (Bourdon, Olson, Backus, Richter, Davis, & Schneeman, 2001). A three-month supplementation of two different dosages of oat β-glucan within an energy restricted diet did not result in greater increases to fasting plasma CCK compared to energy restriction alone and did not benefit weight loss (Beck, Tapsell, Batterham, Tosh, & Huang, 2010).

A study in rats noted that the presence of guar gum and fructo-oligosaccharides within chow reduced *ad libitum* energy intake. This effect was removed when competitive ligands of CCK receptors were given to the animals (Rasoamanana, Chaumontet, Nadkarni, Tomé, Fromentin, & Darcel, 2012), strongly suggesting that the impact of fibres was mediated by the action of CCK. However, it must be noted that postprandial plasma CCK concentration was not measured within

this study. Consumption of a standard chow incorporating resistant starch did not impact the food intake of rats who were intraperitoneally dosed with a specific amount of CCK (L. Shen, Keenan, Martin, Tulley, Raggio, McCutcheon, et al., 2009), suggesting that there was no indirect impact of dietary fibre inclusion on the sensitivity of the test animals to CCK responses.

Secretin is a hormone secreted from the enteroendocrine S cells within the duodenum. Its release causes increases in pancreatic exocrine secretion and is linked to reduction in feelings of hunger and reduced gastric emptying rates (Sekar & Chow, 2013). Secretin is believed to be the first hormone ever to be isolated (Dockray, 2014). Secretin therefore exerts a number of similar roles to those of CCK. Motilin is mainly released from duodenal enteroendocrine cells (Goswami, Tanaka, Jogahara, Sakai, & Sakata, 2015). While secretin tends to reduce gastric emptying, motilin tends to increase pyloric sphincter relaxation to increase flow into the duodenum, with peak motilin concentrations occurring at the same time the gastric phase of digestion is being completed (Ozaki, Onoma, Muramatsu, Sudo, Yoshida, Shiokawa, et al., 2009). Classical studies have highlighted that both hormones are released over a relatively short time frame (less than 30 minutes) in response to intestinal acidification, with secretin reaching a peak faster than motilin and maintaining values above baseline levels of a longer period of time (Ozaki, et al., 2009), suggesting that their actions are not necessarily in direct competition with each other. A range of other peptides released from the small intestinal mucosa, including vasoactive intestine peptide, neurotensin and gastric inhibitory peptide are also believe to play roles in the regulation of the intestinal phase of digestion

Long-term incorporation of various types of dietary fibre in animal feeds have been suggested to increase pancreatic exocrine secretion in response to secretin stimulation (Low, 1989; Sommer & Kasper, 1984; Stock Damge, Bouchet, & Dentinger, 1983). Three-week supplementation of pectin or cellulose did not impact on fasting or postprandial motilin levels in comparison to a (low fibre) control diet (Schwartz, Levine, Singh, Scheidecker, & Track, 1982). A study in type II diabetics noted consumption of 15 g a day of guar gum over a two-week period resulted in a blunting the gastric inhibitory peptide response and an increased output of motilin (Requejo, Uttenthal, & Bloom, 1990).

Dietary fibre and ileocaecal flow

The ileal brake reflex is a mechanism by which the flow of digesta into the large intestine can be limited (Maljaars, Peters, Mela, & Masclee, 2008). It appears as though this mechanism is driven by the release of glucagon-like peptide-1 (GLP-1 and Peptide YY (PYY) from the enteroendocrine L cells in the terminal ileum (Joshi, Tough, & Cox, 2013). Classical work highlighted how the ileal brake mechanism could be triggered by fat reaching/being instilled the terminal ileum (Spiller, Trotman, Adrian, Bloom, Misiewicz, & Silk, 1988; Spiller, Trotman, Higgins, Ghatei, Grimble, Lee, et al., 1984). However, a more recent study suggests that this effect can also be triggered in healthy adults by the instillation of proteins and sugars into the ileum (Van Avesaat, Troost, Ripken, Hendriks, & Aam, 2015) and is more dependent on the total amount of macronutrient energy instilled into the terminal ileum than the source of energy, suggesting that L cells are sensitive to a broad range of luminal factors. Recent evidence would also suggest that the two separate gene products are expressed and produced by the same cells in humans (Habib, Richards, Rogers, Reimann, & Gribble, 2013).The ileal brake mechanism is thought to maximise the small intestinal absorption of a number of nutrients and may be a key component to the "salvage" of digested macronutrients that have escaped absorption proximally in the intestine (Maljaars, Peters, Mela, & Masclee, 2008; Van Avesaat, Troost, Ripken, Hendriks, & Aam, 2015). A continuation of GLP-1 and PYY release occurs

from colonic X and Y cells but plasma concentrations appear to not reach the same peaks as when digesta is in the ileum (Johansson, Nilsson, Östman, & Björck, 2013). Fibres may have indirect effects on the control of the ileal brake mechanism, such as binding to nutrients or reducing their ability to diffuse towards the enteroendocrine cells. However, with the recent observation that free fatty acid receptors are found in the terminal ileum (in rats at least), it has also been postulated that the production of short-chain fatty acids from microbial degradation of fibres could elicit the same reflex action (Darzi, Frost, & Robertson, 2011) through a different secondary effect of fermentable fibre intake.

A range of previous studies in human participants have highlighted that the acute impact of inclusion many types of dietary fibre in a meal tends to prolong the postprandial peak of GLP-1 and PYY. In previous studies where the postprandial response in both gut hormones was measured, polydextrose and a high fibre barley product were suggested to increase the area under the curve of GLP-1 but not PYY (Ames, Blewett, Storsley, Thandapilly, Zahradka, & Taylor, 2015; Olli, et al., 2015). Other studies have suggested that both postprandial GLP-1 and PYY responses are both elevated as a result of inclusion of arabinoxylan or ispaghula husk in comparison to a low fibre test meal (Karhunen, Juvonen, Flander, Liukkonen, Lähteenmäki, Siloaho, et al., 2010; Lafond, Greaves, Maki, Leidy, & Romsos, 2014). Previous research has also suggested impacts of fibre inclusion on either ileal brake-associated hormone but have only measured outcomes related to either GLP-1 or PYY (Joo, Muraoka, Hamasaki, Harada, Yamane, Kondo, et al., 2015; Klosterbuer, Thomas, & Slavin, 2012; Vitaglione, Lumaga, Stanzione, Scalfi, & Fogliano, 2009) and not both. However, due to the prolonged time it takes for digesta to pass through the ileocaecal valve and PYY/GLP-1-producing cells occurring in both the terminal ileum and colon, it is difficult to separate the impact of dietary fibres on the ileal brake mechanism in the absence of parallel estimates of ileocaecal transit. One previous study noted an increased peak in GLP-1 and overall response (as assessed by area under the curve) within the timescale prior to ileocaecal emptying, as estimated by appearance of breath hydrogen peaks (Johansson, Nilsson, Östman, & Björck, 2013).

Longer-term studies have noted that increased habitual fibre intake (β-glucan or high viscosity β-glucans) over 3 to 14 weeks appeared to cause an increase in fasting GLP-1 and PYY concentrations (Beck, Tapsell, Batterham, Tosh, & Huang, 2010; Greenway, O'Neil, Stewart, Rood, Keenan, & Martin, 2007; Reimer, Pelletier, Carabin, Lyon, Gahler, Parnell, et al., 2010). It is possible that changes to fasting concentrations of GLP-1 and PYY are more driven by changes to colonic L cells secretion than those from the terminal ileum. Nonetheless, these findings could also suggest that longer-term there is a need for an increased threshold of PYY and GLP-1 to be met to result in the triggering of the ileal brake mechanism.

Dietary fibre and the small intestinal epithelium

The small intestine is the longest part of the gastrointestinal tract and has by far the largest surface area (Helander & Fändriks, 2014). As a result, it is the major site of absorption of nutrients in humans (Schulze, 2015). Absorptive cells are the major cell type that occurs within the epithelium produced by the differentiation of stem cells that reside towards the base of the crypt of Lieberkuhn (Marshman, Booth, & Potten, 2002). The crypt-villus unit is often considered the functional unit of the small intestine (Marshman, Booth, & Potten, 2002). A recent study noted that exposing cell cultures to an intestine-like milieu within a microchannel device appeared to result in the spontaneous production of structures resembling intestinal villi within the monolayer (H. J. Kim &

Ingber, 2013), suggesting that exposure to the luminal environment is vital in the development and regulation of the mucosal structure.

Other cell types within the small intestinal epithelium include goblet cells (that produce a protective mucus barrier) (Hino, Takemura, Sonoyama, Morita, Kawagishi, Aoe, et al., 2012), Paneth cells (that act in both sensing and defence roles) (Roth, Franken, Sacchetti, Kremer, Anderson, Sansom, et al., 2012) and enteroendocrine cells (key in sensing the chemical composition of the intestinal milieu) (Egerod, Engelstoft, Grunddal, Nøhr, Secher, Sakata, et al., 2012; Formeister, Sionas, Lorance, Barkley, Lee, & Magness, 2009). A morphologically distinct cell type that appears to have secretory roles (the tuft cells) have also been recently identified across the entire intestinal epithelium. While they appear to have a secretory role, their exact role is not well characterised (Gerbe, Legraverend, & Jay, 2012; Gerbe, Van Es, Makrini, Brulin, Mellitzer, Robine, et al., 2011). Intestinal M cells are believed to be a class of distinct cells that are spread diffusely across the small intestinal epithelium. Their major role is believed to be in the sampling and presentation of luminal content to the underlying lymphoid tissue, thereby acting as the epithelial gateway to the intestinal and systemic immune systems (Lopes, Abrahim, Cabral, Rodrigues, Seiça, de Baptista Veiga, et al., 2014).

A large body of work is currently on-going to understand the gene protein factors that regulate the differentiation of small intestinal stem cells to produce an appropriate cross-section of healthy daughter cells (Al Alam, Danopoulos, Schall, Sala, Almohazey, Fernandez, et al., 2015; Formeister, Sionas, Lorance, Barkley, Lee, & Magness, 2009; Melendez, Liu, Sampson, Akunuru, Han, Vallance, et al., 2013; Middendorp, Schneeberger, Wiegerinck, Mokry, Akkerman, Van Wijngaarden, et al., 2014; Yamada, Kojima, Fujimiya, Nakamura, Kashiwagi, & Kikkawa, 2001). However, there is currently limited understanding of how luminal content (driving chemical, immunological or shear-stress changes to the underlying tissues) could affect these key intracellular regulatory pathways. recent evidence has suggested one potential impact of dietary fibre intake on intestinal stem cell activity could be mediated though microbial Short-chain fatty acid (SCFA) production (Petersen, Reimann, Bartfeld, Farin, Ringnalda, Vries, et al., 2014), although due to the relatively low amounts of SCFA produced in the small intestine, this is potentially more significant to differentiation within colonic crypts. Some evidence from organoid models of small intestinal crypts has suggested that stem cells already have been programmed to have specific functionality prior to reaching their final location. The authors concluded that this suggests that luminal content does not have an impact on the fate of the cells (Middendorp, et al., 2014). While this may be true of transient changes within the luminal content, it is still likely that the programming of stem cell is still impacted on by the long-term intestinal milieu. However, cultured cell/organoid work does not allow the complex interplay between different tissues and organs and animal-based studies would be difficult to apply to elucidating mechanistic pathways. Further work is clearly needed within this area. Consideration of the impact of the influence of individual luminal factors on stem cell differentiation would be a sound initial approach but further consideration should also be given for how the myriad of luminal agents interact with each other, which will be challenging to model in cell culture based systems.

Absorption across the small intestinal epithelium occurs through a number of processes; passive diffusion, carrier mediated diffusion, active transport and pinocytosis (a form of non-specific endocytosis), with the major cell type being involved in this role often termed "enterocytes". These absorptive cells are the common cell type found within the small intestinal epithelium. Their roles in absorption and completion of the digestive process (through brush-border membrane-bound

enzymes) are integral to the effective functioning of the small intestine. One previous study noted that inclusion of potato fibre into the diets of acrylamide-dosed mice improved the maintenance of enterocyte numbers, among other effects that offset the impacts of toxicity (Dobrowolski, Huet, Karlsson, Eriksson, Tomaszewska, Gawron, et al., 2012).

Recent studies have suggested that dietary restriction (and therefore dietary fibre restriction) of rodents resulted in an overall reduction in small intestinal length alongside morphological and functional changes in the duodenum consistent with a drive for increased absorptive capacity (increased height of villi, decreased enterocyte depth and increased expression of brush border membrane proteins) alongside the occurrence of atrophy of the ileal mucosa (de Oliveira Belém, Cirilo, de Santi-Rampazzo, Schoffen, Comar, Natali, et al., 2015). A reduction in the number of goblet cells was also noted. It is unlikely that these morphological changes are simply a result of reduced dietary fibre intake within the dietary restriction group. However, this study does highlight how important dietary intake appears to be in the regulation of stem cell differentiation within the intestine.

Alongside the secretion of mucin granules, intestinal goblet cells also produce a range of other antimicrobial factors, such as secretory immunoglobulin A (H. Chen, Wang, Degroote, Possemiers, Chen, De Smet, et al., 2015). It has also been recently postulated that goblet cells are directly involved in luminal sampling and the delivery of antigen to the underlying lamina propria and immune response-mediating tissues (Knoop, McDonald, McCrate, McDole, & Newberry, 2015), although this action is more frequently assumed to mediated by enteroendocrine cells. A number of previous animal studies have highlighted how inclusion of different types of dietary fibre with the diet of laboratory animals impacts on the number of goblet cells along the small intestinal epithelium (Hedemann, Eskildsen, Lærke, Pedersen, Lindberg, Laurinen, et al., 2006; Tanabe, Sugiyama, Matsuda, Kiriyama, & Morita, 2005). Such changes can be assessed by histological staining of sections of the mucosa and can give details both on the capacity for the mucosa to secrete mucins (Ito, Satsukawa, Arai, Sugiyama, Sonoyama, Kiriyama, et al., 2009) as well as the charge of the sugar residues on the mucin side chains (Hino, et al., 2012). The inclusion of most types of dietary fibres consistently tends to increase the numbers of goblet cells found in the mucosa in comparison to low fibre or fibre-free controls (Hino, Sonoyama, Bito, Kawagishi, Aoe, & Morita, 2013; Hino, et al., 2012; Ito, et al., 2009). Certain types of fibre, such as isolated cellulose, appear to have minor of no effects on goblet cell numbers, while other fibre types (e.g. arabinoxylans) appear to have a profound effect on goblet cell coverage (100% increase vs control) in the villus and modest impacts (c.25% increase) in the intestinal crypts (H. Chen, et al., 2015).

However, an alteration in goblet cell numbers does not necessarily equate to a change to the physical or functional capacity of the mucus barrier. Due to methodological complexities (Strugala, Allen, Dettmar, & Pearson, 2003), there are relatively few studies that have assessed the impact of different types of dietary fibres on the thickness and functionality of the mucus barrier. A number of other studies have also used immunochemistry or other analytical techniques within animal models to estimate the impact of fibre intake on mucin release into the lumen (Morel, Melai, Eady, & Coles, 2005; Morita, Tanabe, Ito, Sugiyama, & Kiriyama, 2008; Morita, Tanabe, Ito, Yuto, Matsubara, Matsuda, et al., 2006; Tanabe, Ito, Sugiyama, Kiriyama, & Morita, 2006; Tanabe, Sugiyama, Matsuda, Kiriyama, & Morita, 2005). The measured mucin output may relate well to total mucus production but is dependent on the method by which mucins are isolated from tissues. There is a potential for

factors, such as the accidental retrieval of luminally-occurring gastric mucins or unsecreted mucin granules from sloughed cells, cross-reactivity resulting from the diverse nature of factors present in the small intestine and the rate of mucus barrier degradation (affected by other luminal factors) to affect the outcomes of such analytical techniques.

Paneth cells reside at the base of small intestinal crypts are believed to play important roles in the maintenance of the epithelial layer, particularly after insult or injury to the surrounding epithelial cells (Roth, et al., 2012). Work carried out with experimental models of crypts would suggest that Paneth cells are important in the overall functional development of crypt-villus units (Sato, Van Es, Snippert, Stange, Vries, Van Den Born, et al., 2011). Paneth cells have a particularly long life span (around 100 days) compared to other small intestinal cell types (Roth, et al., 2012). Paneth cells produce a gambit of antimicrobial peptides to help protect the intestinal crypts from infiltration by luminal microbes (Sato, et al., 2011). A recent study noted that polysaccharides isolated from squid ink appear to cause upregulation the expression of genes governing these antimicrobial peptides during chemically-induced mucosal injury (Zuo, He, Cao, Xue, & Tang, 2015). This study highlights that other polysaccharides have the potential to impact on Paneth cells directly, although the authors note they cannot find other evidence linking the intake of commonly-consumed dietary fibres to this action.

Enteroendocrine cells contain specific membrane bound protein receptors at act to sense the concentration of specific chemical factors within the small intestinal milieu (Daly, Al-Rammahi, Moran, Marcello, Ninomiya, & Shirazi-Beechey, 2013; Jang, Kokrashvili, Theodorakis, Carlson, Kim, Zhou, et al., 2007; Margolskee, Dyer, Kokrashvili, Salmon, Ilegems, Daly, et al., 2007). As a result of being triggered, enteroendocrine cells release a range of different neurohumoral mediators to effect changes at a local and systemic level via the circulatory system and enteric nervous system (Gribble, 2012).

The commonly accepted model of enteroendocrine cells within the small intestine are that certain cell types produce specific neurohumoral mediators within specific segments (i.e. CCK, secretin and gastric inhibitory peptide within the duodenum and GLP-1 and PYY within the ileum (Egerod, et al., 2012; Habib, Richards, Rogers, Reimann, & Gribble, 2013)). However, a recent study that labelled CKK-producing cells within transgenic mice suggests that co-expression of genes necessary to produce a range of neurohumoral mediators was found both in nascent enteroendocrine cells (occurring within the crypts), alongside mature cells (occurring within the villi) (Egerod, et al., 2012). The authors cannot find evidence of a direct interaction between enteroendocrine cells of the small intestine and dietary fibre. However, as these cells appear to be triggered by the presence of fats, lipids and carbohydrates in the small intestinal, impacts of fibres on binding these substrates or inhibiting the presentation of their products to the intestinal epithelium would be likely to affect neurohumoral responses from the enteroendocrine cells.

A novel cell type (termed tuft cells) was recently found to exist within the small intestinal epithelium (Gerbe, et al., 2011). Tuft cells appear to occur in both the small and large intestine and have a unique morphology and may have roles in both chemosensation, local inflammatory mediation and other possibly other secretory processes (Gerbe, Legraverend, & Jay, 2012; Nakanishi, Seno, Fukuoka, Ueo, Yamaga, Maruno, et al., 2012). The exact role of these cells and the putative impact that dietary fibres may have on their functionality is currently unclear.

The small intestine mucosa contains discrete sites of follicular lymphoid tissue (sometimes referred to as the Peyer's patches) which are in close proximity to the overlying mucosa (Santaolalla & Abreu, 2012). Small intestinal M cells are believed to exist in high numbers in these areas and appear to be the key sites of antigen sampling and presentation in the small intestine due to their high potential for transcytosis (Lopes, et al., 2014). Previous evidence also exists to suggest that other cells types (i.e. goblet cells and enteroendocrine cells) may also be involved in the process of sampling luminal contents (McDole, Wheeler, McDonald, Wang, Konjufca, Knoop, et al., 2012; Nagatake, Fujita, Minato, & Hamazaki, 2014; Schulz & Pabst, 2013). Within these areas of high M cell density, a number of other specialist cells exist that may also be key to the action of this area for antigen sampling and immunomodulation. Recent work has suggested that dendritic cells, existing in the follicular below the M cells, may actually drive the process of translocation across the epithelium by extending dendrites through specialised channels that run through each M cell (Lelouard, Fallet, De Bovis, Méresse, & Gorvel, 2012).

Previous studies would suggest that micro- or nanoparticles encapsulated with positively charged fibres like chitosan may preferentially bind to intestinal Peyer's Patches M cells (Lopes, et al., 2014; Yoo, Kang, Choi, Park, Na, Lee, et al., 2010), highlighting that the presence of certain types of fibre could influence antigen uptake at the surface of M cells directly. It is also likely that the impact of various fibres on nutrient binding and the small intestinal microfloral community are also likely to affect the processes of these small intestine associated lymphoid tissue, as was recently suggested in a study looking at M cell translocation in the presence of soluble fibres extracted from plantains (Roberts, Keita, Parsons, Prorok-Hamon, Knight, Winstanley, et al., 2013).

Dietary fibre and small intestinal motility

It is often suggested that dietary fibre *per se* tends to slow the rate of transit of digesta along the small intestine. However, previous radiographic studies highlighted how both the form and type of dietary fibre appeared to impact small intestinal motility by estimation of small intestinal transit time. Within these studies, it was noted that coarse bran significantly accelerated small intestinal transit in some participants (as did plastic particles of similar size), while fine bran and ispaghula husk did not have a significant effect (McIntyre, Vincent, Perkins, & Spiller, 1997; Vincent, Roberts, Frier, Perkins, MacDonald, & Spiller, 1995). This previous work also highlighted the complexity of estimation of small intestinal transit time through minimally invasive means. In essence, it is necessary to assess both gastric emptying and colonic filling. As both of these events happen over a long period of time, an assumption must be based on an arbitrary cut-off (the ones used in the previously cited work were 50% of the digesta leaving the stomach and 50% of the digesta entering the large bowel). Other minimally invasive methods that are employed to estimate gastric emptying include paracetamol or synthetic substrate appearance rates in the bloodstream and changes to gastric volume assessed by clinical imaging methods (Kar, Jones, Horowitz, Chapman, & Deane, 2015), while colonic filling can be estimated by appearance of peaks of exhaled hydrogen in the breath (produced by microbial fermentation and transported to the lungs through the systemic circulation) (Bertram, Andresen, Layer, & Keller, 2014; Bianchi & Capurso, 2002), or more directly by clinical imaging (Camilleri, Iturrino, Bharucha, Burton, Shin, Jeong, et al., 2012) and the use of swallowed devices (WorsØe, et al., 2011).

The inclusion of 5 g of guar gum in solid or liquid meals appeared to increase the time length over which the small intestine was motile in comparison to control meals (V. Schönfeld, Evans, & Wingate, 1997). Within this study, guar gum did not seem to affect the frequency or intensity of

contraction within the small intestine. The effect also seemed to be dependent on the presence of other nutrients, as inclusion of guar gum within water did not increase motility compared to a fibre-free water control and also had much less impact on motility than control or guar-containing meals. A separate study that assessed the impact of different dosages of guar gum (0 to 4.5 g - provided within a viscous meal) suggested that guar viscosity did not impact on estimated small intestinal transit time (Van Nieuwenhoven, Kovacs, Brummer, Westerterp-Plantenga, & Brouns, 2001), although it must be noted that all intestinal transit times measured within this study were very short (around 150 minutes on average). This could have been due to the addition of lactulose to estimate orocaecal transit time but which may have also caused a decrease within the habitual, non-experimental, transit time of the individuals (Carlin & Justham, 2011; Wirz, Nadstawek, Elsen, Junker, & Wartenberg, 2012).

Evidence from animal studies would suggest that long-term intake of dietary fibre also causes the muscular layer of the small intestine to become thicker (Ma & Zhang, 2003; Stark, Nyska, & Madar, 1996), although this would be challenging to evidence in humans. The ileal smooth muscle of guinea pigs fed diets containing various convenience foods appeared to be less sensitive to electrical stimulation in the brown rice congee group compared to the white rice congee and baked bean-fed groups (Patten, Bird, Topping, & Abeywardena, 2004). This could suggests that insoluble fibres affect the contractile nature of smooth muscle but it must be noted that the incorporation of the convenience foods into the guinea pig diets only accounted for a very small proportion of the total dietary fibre.

Dietary fibre and changes to small intestinal morphology and absorptive capacity

The inclusion of pectin to the diets of pigs fed over a 9-day period resulted in a reduction in the average villous height and an increase in the number of villi per unit area sampled at two site on the small intestine (Hedemann, et al., 2006). For a longer study (3 months feeding – also carried out in pigs), there appeared to be no effect of inclusion of 5.2% fibre (mainly pea fibre and pectin) on the overall length of the small intestine versus a low fibre control (Jørgensen, Zhao, & Eggum, 1996). Differential effects of different types of dietary fibre on small intestinal crypt-villus height have also been frequently noted in rodent models (Gomez-Conde, Garcia, Chamorro, Eiras, Rebollar, Pérez De Rozas, et al., 2007; H. S. Shen, Chen, Wu, Li, & Zhou, 2012). These findings perhaps highlight that dietary fibre could act, both directly (through the mechanical activation of intestinal stretch receptors) or indirectly (through actions on the small intestinal microflora or by binding to nutrients or exocrine secretions). Previous studies feeding fibre to germ-free and conventional mice, suggested that microbial fermentation in the small intestine was an important driver of these changes to mucosal morphology (Goodlad, Ratcliffe, Fordham, & Wright, 1989).

Previous evidence suggests that soluble, gel-forming dietary fibres would be expected to reduce the intestinal absorption of other dietary factors. Evidence exists to suggest that fibre types such as alginate (Wilcox, Brownlee, Richardson, Dettmar, & Pearson, 2014), guar gum (Ou, Kwok, Li, & Fu, 2001) and other fibre isolates could affect changes that limit the rate of nutrient digestion/absorption in the small intestine (Fabek, Messerschmidt, Brulport, & Goff, 2014; Zacherl, Eisner, & Engel, 2011). In the case of certain nutrients, this action has been suggested to be linked to improved health (e.g. glucose, cholesterol and dietary fats) via mechanisms of delayed postprandial appearance in the plasma (Ou, Kwok, Li, & Fu, 2001; Wilcox, Brownlee, Richardson, Dettmar, & Pearson, 2014; Zacherl, Eisner, & Engel, 2011), while others are considered as being potentially

negative, particularly in the case of fibres that might bind to essential minerals (Elhardallou & Walker, 1999; Wong & Cheung, 2005). In most cases, these methods have modelled the acute effect of meal consumption *in vivo* or *in vitro* and do not consider long-term health or nutrient status. It is possible reduced absorption in the small intestine might be expected to increase the salvage of nutrients in the colon (Miyada, Nakajima, & Ebihara, 2012) or lead to longer-term changes in absorptive capacity in the small intestine, such as increased crypt-villus depth and epithelial surface area (as discussed above).

Consumption of dietary fibre may also lead to molecular changes to the epithelial organisation. In previous intestinal permeability studies, it was noted that inclusion of inulin within a pasta resulted in a reduction of intestinal permeability (assessed by urinary lactulose-mannitol excretion) versus a control pasta in a double-blind, crossover study (Russo, Linsalata, Clemente, Chiloiro, Orlando, Marconi, et al., 2012), believed to be a result of a reduction in the circulating levels of zonulin, a protein that can act to disassemble tight junctional complexes along the gut epithelium (Asmar, Panigrahi, Bamford, Berti, Not, Coppa, et al., 2002) and an increase in circulating GLP-2, which is believed to increase the number of absorptive cells within the mucosa (Sangild, Tappenden, Malo, Petersen, Elnif, Bartholome, et al., 2006). In short-term (9 days) feeding studies in pigs, it was noted that high fibre diets increased the activity of brush-border bound disarrachidases isolated from the small intestinal mucosa (Hedemann, et al., 2006). This is likely to be due to an increase in expression of the enzymes, which could be suggestive of either an increased availability of disaccharides in the small intestine, or an attempt by the intestinal epithelium to increase its absorptive potential, similar to how the number of intestinal iron transport proteins have been reported to increase in response to a low iron diet (Zoller, Koch, Theurl, Obrist, Pietrangelo, Montosi, et al., 2001).

Dietary fibre and small intestinal exocrine secretions

Although the small intestine is the major site of macronutrient digestion within the human gut, the majority of enzymes it produces appear to be membrane-bound. Enteropeptidase (also known as enterokinase) is believed to be one of these membrane-bound entities (Long Zheng, Kitamoto, & Evan Sadler, 2009; Song, Choi, & Seong, 2002) that could also be released within the intestinal juice (succus entericus) from the crypts of Lieberkühn. mRNA studies suggest that enteropeptidase is produced by both enterocytes and goblet cells within the normal human duodenum (Imamura & Kitamoto, 2003). Enteropeptidase has a very high specificity for cleaving the tetra aspartyl-lysil sequence that occurs within the trypsinogen chain (Mikhailoya & Rumsh, 2000). This results in the production of the active form (trypsin) that drives the cleavage of other zymogens released within the pancreatic exocrine secretion (Simeonov, Zahn, Sträter, & Zuchner, 2012) and is the key step in intestinal protein digestion (J. M. Chen, Kukor, Le Maréchal, Tóth, Tsakiris, Raguénès, et al., 2003).

The authors are aware of only one study that has looked at the impact of dietary fibre on enteropeptidase activity. Within this study, it was noted that a range of very different fibre preparations (wheat bran, guar gum, ispaghula husk, cellulose and lignin) had no measureable impact on the activity of free enteropeptidase in solution (Hansen, 1986). It could be postulated that this is down to the high specificity of enterokinase to its substrates. However, future studies into how different dietary fibres could affect diffusion of substrates (such as trypsinogen) to the brush border (or other models including membrane-bound enteropeptidase) would also be valuable in understanding how different types of fibres could affect this key activation process.

The major exocrine secretion that the intestinal epithelium produces is the functional bilayer of mucus (Allen & Flemström, 2005) that protects the underlying mucosa from shear stress and chemical, microbial or enzymatic degradation (Atuma, Strugala, Allen, & Holm, 2001). This functional is hypothesised to be selectively permeable so as to allow diffusion of nutrients and substrates for the brush border-bound enzymes to the epithelial surface (Macierzanka, Mackie, Bajka, Rigby, Nau, & Dupont, 2014). The adherent and loosely adherent mucus layers have been measured (in anaesthetised rats) to be much thinner than the mucus that covers the stomach and large intestine (Atuma, Strugala, Allen, & Holm, 2001) and therefore uptake is affected by the thickness and constitution of the unstirred layer.

Alongside having impacts on the secretion of mucus/mucins, it also appears that dietary fibres could have direct actions on the rheological properties of the function mucus barrier. Previous studies suggested that gel-forming fibres (guar gum and carboxymethylcellulose) could limit the absorption of glucose within excised sections of rat jejunum, possibly by affecting the mucus barrier function (Johnson & Gee, 1981).

Dietary fibre and pancreatic exocrine physiology

Due to the spectrum of digestive enzymes secreted by the pancreas (Christiansen, Backensfeld, & Weitschies, 2010; Layer & Keller, 1999) and the proportionate contribution of these enzymes to human digestive processes (Kammlott, Karthoff, Stemme, Gregory, & Kamphues, 2005; Lindkvist, 2013), pancreatic juice could be considered the single most important digestive secretion in healthy adults. A sizeable body of evidence has been accumulated that isolated dietary fibre fractions can modulate the activity of pancreatic enzymes *in vitro*, as summarised in Table 1. Previous evidence suggests that fibre isolates do not have the same impact on all isolated digestive enzymes , which could be based either on specificity or interference with other factors involved in catalytic activity, such as free cations and hydrogen ions, or the availability of co-factors (Dukehart, Dutta, & Vaeth, 1989). Table 1 below summarises some of the in vitro evidence that different fibre fractions affect digestive enzyme activity.

[Table 1 here]

The potential for some fibres to impact on the enzyme activity of specific digestive enzymes suggests the potential for targeted therapeutic roles. For example, reduction of pepsin activity has been suggested as a potential therapy for gastrointestinal reflux (Strugala, Kennington, Campbell, Skjåk-Bræk, & Dettmar, 2005) but at the same time, total inhibition of protease activity might be expected to have negative consequences on amino acid absorption (Lindkvist, 2013). Previous work suggested that specific alginate fractions could inhibit pepsin activity but not trypsin activity (Chater, Wilcox, Brownlee, & Pearson, 2015).

Inhibition of pancreatic lipase by high intake of specific types of dietary fibre could be responsible for fibre-induced steatorrhea (Roerig, Steffen, Mitchell, & Zunker, 2010). Previous studies suggested that high fibre diets accentuate fat malabsorption in patients with pancreatic insufficiency - high fibre intake was associated with a 32% increase in faecal fat excretion in a group of 12 patients (Dutta & Hlasko, 1985). Conversion from an omnivorous to a vegan diet (which significantly increased fibre intake) over a 6-week period altered the faecal output of some proteases but did not cause a measurable change in lipase activity (Walkowiak, Mądry, Lisowska, Szaflarska-Popławska, Grzymisławski, Stankowiak-Kulpa, et al., 2012). This effect could also have been driven by a lower

intake of protein in the vegan versus omnivorous dietary pattern. Inclusion of generic alginate preparations within test meals was evidenced to increase fat excretion and attenuation of circulating post-prandial blood lipids in ileostomists (Sandberg, Andersson, Bosœus, Carlsson, Hasselblad, & Härröd, 1994). This could be due to the previous *in vitro* observation that some alginates can reduce pancreatic lipase activity (Wilcox, Brownlee, Richardson, Dettmar, & Pearson, 2014). Pancreatic lipase-specific inhibition has been suggested as a means that other fibres, such as chitosan could be used as weight loss therapies (Gades & Stern, 2003). Currently, evidence for efficacy of this mode of therapy only exists for pharmacological agents like orlistat in long-term weight loss studies(Douglas, Bhaskaran, Batterham, & Smeeth, 2015).

While it is well established that dietary fibres have modulatory effects on the activity of digestive enzymes once they have entered the intestinal lumen. It is however less clear how dietary fibre modulates pancreatic exocrine secretions. Although evidence suggests that acute ingestion of dietary fibre can lead to inhibition of digestion, there is evidence to suggest that sustained intake of dietary fibre can lead to pancreatic compensation with increased secretion of digestive enzymes. Previous studies in pigs have suggested that potato fibre consumption result in an increased pancreatic exocrine secretion with increased lipolytic, proteolytic and amylolytic activity (Jakob, Mosenthin, Thaela, Weström, Rehfeld, Olsen, et al., 2000). Sustained, increased inclusion of dietary fibre in the diets of rodents has also been suggested to increase pancreatic exocrine secretions (Liener & Hasdai, 1986; Schneeman, Richter, & Jacobs, 1982), although it is uncertain whether this effect is mediated by fibre directly inhibiting digestive enzyme activity, or whether this is a result of the presence of increased phytochemical inhibitors (e.g. of trypsin activity) within such feeds.

It is thought that dietary fibre interferes with the negative feedback regulation of pancreatic enzyme secretion leading to increased pancreatic exocrine function. Levels of pancreatic exocrine secretion have been evidenced to be regulated by intraluminal enzyme concentration through oral or duodenal addition of enzymes (Morisset, 2008; Walkowiak, Witmanowski, Strzykala, Bychowiec, Songin, Borski, et al., 2003). It was previously observed that participants fed a diet supplemented with 20g/day fibre for 4 weeks increased total postprandial pancreatic lipase output (Dukehart, Dutta, & Vaeth, 1989).

Dietary fibre and hepatic exocrine secretion

The liver is a multifunctional organ that is key in the storage and handling of nutrients absorbed by the gut (Kullak-Ublick, Beuers, & Paumgartner, 2000). The major role that the liver plays in digestion is through the production of bile, which is key to the process of triglyceride digestion through pancreatic lipase activity (Wilde & Chu, 2011).

In humans, bile is secreted by hepatocytes into a series of canaliculi which eventually drain into the gall bladder through the common hepatic duct where it is subsequently stored (Boyer, 2013). During this storage, the bile is further processed within the gall bladder, where large proportions of bile water can be reabsorbed over prolonged periods of retention (van Erpecum, 2005). Bile aids the digestion of dietary fats through the detergent effect of bile acids and bile salts, thereby dispersing dietary fats into mixed micelles and increasing the surface area upon which digestive lipases can act (Torcello-Gómez, Maldonado-Valderrama, de Vicente, Cabrerizo-Vílchez, Gálvez-Ruiz, & Martín-Rodríguez, 2011; Wilde & Chu, 2011).

Bile acids are cholesterol derivatives. Within healthy humans, the dominant forms of secreted bile acids are believed to be cholic and chenodeoxycholic acid, with almost all molecules conjugated to glycine (75 %) and taurine, existing either as bile salts (in combination with sodium or potassium) or bile acids (Pearson, Parikh, Orlando, Johnston, Allen, Tinling, et al., 2011), although there is also clear evidence that the proportion of these bile acids having high intra- and inter-individual variability (Brockerhoff, Höckel, Holtermüller, Köhl, Weis, & Rathgen, 1982; Duane, 1994; Hanson & Duane, 1994). In the terminal ileum, a large proportion of secreted bile acids (>90 %) are reabsorbed (by specific bile acid transporters) and recycled via the hepatic portal vein to the liver where they are reutilised (Zhou, Levin, Pan, McCoy, Sharma, Kloss, et al., 2014). Bile mixes with pancreatic exocrine secretions in the ampulla of Vater, where the pancreatic duct and common bile duct merge (Blidaru, Blidaru, Pop, Crivii, & Seceleanu, 2010). A small amount of secondary bile acids are produced by bacterial metabolism within the small intestine. Secondary bile acids are produced in much higher amounts in the large intestine and high faecal, biliary or circulating levels of these metabolites are associated with increased risk of colorectal cancer and gallstone formation (Ridlon, Kang, & Hylemon, 2006).

A number of previous studies have assessed the impact of dietary fibre fractions on adsorption of bile acids which would be expected to limit the reuptake of bile acids within the terminal ileum and thereby drive the need for further production of bile acids within the liver, thereby hypothetically positively affecting plasma cholesterol profiles and utilising stores of saturated fatty acids within the liver (Cornfine, Hasenkopf, Eisner, & Schweiggert, 2010; Daou & Zhang, 2014; Kanauchi, Serizawa, Araki, Suzuki, Andoh, Fujiyama, et al., 2003; Peerajit, Chiewchan, & Devahastin, 2012; Sreenivas & Lele, 2013; Takekawa & Matsumoto, 2012; Torcello-Gómez & Foster, 2014; N. Zhang, Huang, & Ou, 2011). It must be noted that previous *in vitro* studies on purified bile acids highlights that this action is as dependent on the structure and presence of conjugate amino acids greatly affects the interactions with isolated fibre fractions (Araki, Mukaisho, Fujiyama, Hattori, & Sugihara, 2012; Beysseriat, Decker, & McClements, 2006; Gao, Yan, Xu, Ye, & Chen, 2015; Górecka, Dziedzic, & Hęś, 2014; Torcello-Gómez, Fernández Fraguas, Ridout, Woodward, Wilde, & Foster, 2015; W. Wang, Yoshie, & Suzuki, 2002).

Dietary fibre and diseases of the small intestine, liver and exocrine pancreas

Epidemiological evidence linking dietary fibre intake to diseases of the small intestine and its accessory organs appears to be relatively limited in scope, as outlined by recent studies (post 2000) in Tables 2 and 3. This may be appropriate in certain cases, where the disease aetiology is well evidenced to be communicable (e.g. hepatitis) or as a result of the intake of other dietary factors (e.g. some forms of liver cirrhosis and excessive alcohol intake) (Lachenmeier, Kanteres, & Rehm, 2011). In other cases, where disease prevalence may be increasing worldwide and aetiology is less well defined (e.g. non-alcoholic fatty liver disease), this highlights a potential research gap that future studies could attempt to address. Due to the large number of up-to-date guidelines, meta-analyses and reviews already are in existence on the association of dietary fibre intake with type II diabetes (e.g. (Ajala, English, & Pinkney, 2013; Boeing, Bechthold, Bub, Ellinger, Haller, Kroke, et al., 2012; Franz, Powers, Leontos, Holzmeister, Kulkarni, Monk, et al., 2010; Lattimer & Haub, 2010)) and obesity/metabolic syndrome (e.g. (Abete, Astrup, Martínez, Thorsdottir, & Zulet, 2010; Boeing, et al., 2012; Catapano, Reiner, De Backer, Graham, Taskinen, Wiklund, et al., 2011; Perk, De Backer, Gohlke, Graham, Reiner, Verschuren, et al., 2012)), these health conditions are omitted from the current review.

[Tables 2 and 3 near here]

Non-alcoholic fatty liver disease is defined as the excess build-up of parenchymal fat in the liver in the absence of excessive habitual alcohol consumption (Than & Newsome, 2015). A recent observational study suggested no association of dietary intake with markers of severity of non-alcoholic fatty liver disease (Ricci, Canducci, Pasini, Rossi, Bersani, Ricci, et al., 2011), highlighting the need for larger, longer-term studies in the future. Such studies may be challenging using existing longitudinal datasets, as non-alcoholic fatty liver disease diagnosis has been historically difficult and the condition is associated with many co-morbidities (Abd El-Kader & El-Den Ashmawy, 2015). One previous study in a small cohort (n = 12) of patients noted that compared intake of a Mediterranean diet to a low fat, high carbohydrate diet in a randomised, crossover trial. While both groups lost weight, a larger reduction in liver fat content and a greater improvement in insulin sensitivity were noted in the Mediterranean diet treatment arm. Dietary fibre intake significantly increased (by an average of almost 9 g per day from a high baseline intake of 27.6 g/day) from the baseline/washout dietary period in the participants receiving the Mediterranean Diet but not the low fat high carbohydrate diet. It must be noted that other dietary factors with potential to affect the study outcomes, such as the percentage of energy from each macronutrient and fatty acid profiles were also significantly altered within these treatment arms, so these findings are unlikely to be due simply to changes in fibre intake.

Despite a large number of studies focusing on other hepatic conditions and dietary fibre intake, there seems to be no available evidence to consider an association between fibre intake and risk of liver cancer. A number of previous studies have looked at how other dietary factors may be associated with risk of hepatocarcinoma and these findings have been reviewed fairly recently (Gomaa, Khan, Toledano, Waked, & Taylor-Robinson, 2008) but it appears that only two studies have previously evaluated the association of dietary fibre/fruit and vegetable intake with hepatic cancer. This is surprising due to the recent increase in prevalence of liver cancer (Bosch, Ribes, Díaz, & Cléries, 2004). This is in contrast with the number of articles linking dietary fibre to pancreatic cancer (see Table 2), where prevalence is both lower than hepatic cancer in developed countries and has tended to remain relatively stable over time (Lowenfels & Maisonneuve, 2006).

Small intestinal cancer incidence is around 30 times less frequent than colorectal cancer in both men and women in the US (Schatzkin, Park, Leitzmann, Hollenbeck, & Cross, 2008). Although the small intestine makes up a large proportion of the gastrointestinal tract by length, the low incidence may be in part due to relatively short exposure time to potential carcinogens compared to the large bowel (Lee, Erdogan, & Rao, 2014), as well as the relatively high water content of the digesta within the small intestine (Chowdhury, Murray, Hoad, Costigan, Marciani, Macdonald, et al., 2014), thereby diluting harmful factors of dietary and endogenous origin.

Pancreatitis broadly refers to inflammation of the pancreas and is believed to be caused by multiple aetiologies (Artifon, Chu, Freeman, Sakai, Usmani, & Kumar, 2010). A randomised, double-blinded parallel trial in a sample (n = 30) of Turkish patients with acute pancreatitis (Karakan, Ergun, Dogan, Cindoruk, & Unal, 2007) noted that patients who received 24 g/day of mixed soluble and insoluble fibre within their nasojejunal feeds reduced the length of total hospital stay by a median of 5 days, compared to median stay length of 15 days for the control group who received only standard enteral feeds. The frequency of serious complications was also reduced in the fibre group (7 of 15 patients versus the 9 of 15 control patients). While the authors inferred that this was down to the "prebiotic"

impact of the fibre supplementation, this effect was not evidenced by any microbial data and further detail of the fibre supplementation (other than the formulation containing 47% soluble fibres) was not reported. A previous meta-analysis that compared the impact of inclusion of probiotic formulations and fibres to enteral feeds noted no improvement in pancreatitis patient outcome compared with control treatments only supplemented with fibre (Petrov, Loveday, Pylypchuk, McIlroy, Phillips, & Windsor, 2009), which further suggests that any positive impact that fibre inclusion may have on pancreatitis outcomes appears to not be due to microfloral mediation.

Summary

The above evidence (see Table 2 and 3) highlights that a lack of quality observational studies carried out on dietary fibre/fibre-rich food intake and diseases of the small intestine, pancreas and liver. In some cases, this is surprising considering the high prevalence of these diseases/dysfunctions. Isolated fibres from varying sources have different impacts on the activity of enzymes involved in the intestinal phase of digestion, although this effect does not simply seem to be a result of viscosity or gel-forming nature. This action is likely to impact enteroendocrine cell-mediated signalling in the gut which may further result in differential effects of fibres on intestinal motility and exocrine secretion into the intestine.

In vivo studies in animals currently point to the potential of incorporation of certain fibre types in foods or supplements to manage body weight. *In vitro* evidence (see Table 1) would provide potential mechanisms through which intake of dietary fibres could impact energy absorption in the small intestine. Limited evidence from intervention-based studies hampers the potential for health claims in relation to specific fibre fractions and weight loss (Poddar, Kolge, Bezman, Mullin, & Cheskin, 2011; Wanders, van den Borne, de Graaf, Hulshof, Jonathan, Kristensen, et al., 2011) Further from this, development of high fibre products targeted at benefitting various health outcomes can be hampered by poor palatability of high fibre products (van Kleef, van Trijp, van den Borne, & Zondervan, 2012), technical issues with industrial scale production of foods with higher fibre content and limited potential of many fibre-fortified foods to provide a relevantly high amount of dietary fibre to the consumer to cause the desired effects at each meal. Even if a highly acceptable product is developed, there is still the potential that incorporation of high amounts of fibre isolates within the diet could lead to unwanted gastrointestinal consequence, such as steatorrhea or altered whole gut transit times (resulting in constipation or diarrhoea).

There is also a drive by public health agencies around the world to increase the dietary intake of fibre-rich foods, such as fruits, vegetables and whole grains at a population level within an ideal diet and lifestyle template. The above evidence highlights that different plant foods or fibre isolates appear to have differential effects on small intestinal physiology. There is currently no good evidence to support the notion that fibre supplementation with fibre isolates to meet daily recommendations should replace an overall sound dietary pattern based in on intake of fibre-rich foods. While isolated fibres may have impacts that would be expected to be beneficial to health, impacts on specific, long-term health outcomes must be better evidenced using highly acceptable, well-focused food products in appropriately designed clinical trials.

Acknowledgements

Table 1: Summary of the impact of selected types of isolated dietary fibre on the activity of pepsin, trypsin, pancreatic α-amylase and pancreatic lipase. Activity Relative to 100% control.

Fibre	Additional Notes on source and characteristics of fibre	Percentage Activity Relative to 100% control					Source	Notes on methodology
		Amylase	Pepsin	Lipase	Trypsin	Chymotrypsin		
Pectin	Lemon	64.8 [a, 1, α]	67 [b, 2, α]	-	71.9 [c, 3, α]	74.7 [c, 4, α]	(K. Ikeda & Kusano, 1983)	*Substrate:* a - Soluble starch
	Apple	50.7 [a, 1, α]	42.6 [b, 2, α]	-	52.4 [c, 3, α]	72.8 [c, 4, α]	(K. Ikeda & Kusano, 1983)	b – Casein c - BTpNA - Benzoyl-L-trypsin p-nitroanilide
	Citrus	169.6 [5, β]		123.4 [5, β]	100.8 [5, β]	128.3 [5, β]	(Dunaif & Schneeman, 1981a, 1981b)	d – Succinyl albumin e - 1,2 Di-o-lauryl-rac-glycero-3-(glutaric acid 6-methyl resorufin ester) (DGGR)
	Citrus (mw ~750k)	-	-	~30 [10, f, α]	-	-	(Tsujita, Sumiyoshi, Han, Fujiwara, Tsujita, & Okuda, 2003)	f - Trioleoylglycerol
	Citrus (mw ~750k)	-	-	80 [10, f, ζ]	-	-	(Edashige, Murakami, & Tsujita, 2008)	g –Corn oil emulsion h - β-Lactoglobulin
	Citrus (Low mw)	-	-	60 [10, f, ζ]	-	-	(Edashige, Murakami, & Tsujita, 2008)	I – Encapsulated egg yolk J - Maize starch (MS)
	Citrus (High mw)	-	-	20 [10, f, ζ]	-	-	(Edashige, Murakami, & Tsujita, 2008)	K – Potato starch J - Triolein L – Corn starch M – Tributyrin
	No additional information (NAI)	-	-	~64 [12, g, η]	-	-	(Espinal-Ruiz, Parada-Alfonso, Restrepo-Sánchez, Narváez-Cuenca, & McClements, 2014)	*Enzyme* 1 - Amylase from bacillus subtilis 2 - Pepsin from hog stomach mucus

Group	Description						Reference
	LM Pectin	-	104.4 [h, 13, θ]	-	← 55.0 [h, 14+15, θ] →		(Mouécouou, Sanchez, Villaume, Marrion, Frémont, Laurent, et al., 2003)
	Citrus fruits - galacturonic acid content 86.3%, methoxy content 8.9%	-	-	80.8 [M, 23, Λ]	-		(O'Connor, Sun, Smith, & Melton, 2003)
Alginate	Sodium alginate	67.5 [a, 1, α]	>100 [b, 2, α]	-	78.5 [c, 3, α]	54.4 [c, 4, α]	(K. Ikeda & Kusano, 1983; K. K. Ikeda, T, 1983)
	Alginates varying in M:G content from F[G]=0.34-0.68	-	53.9-88.6 [d, 6, α]	-	88.5-110.3 [d, 7, α]	-	(Chater, Wilcox, Brownlee, & Pearson, 2015)
	As above	-	19.42-60.84 [d, 1, δ]	-	-	-	(Strugala, Kennington, Campbell, Skjåk-Bræk, & Dettmar, 2005)
	As above	-	-	27.8-102.3 [e, 9, ε]	-	-	(Wilcox, Brownlee, Richardson, Dettmar, & Pearson, 2014)
Fucoidan	Extracted from *F. vesiculosus*	100 [a, 17, o]	-	-	-	-	(K. T. Kim, Rioux, & Turgeon, 2014)
	Extracted from *A. nodosum* at varying harvesting periods	0-93 [a, 17, o]	-	-	-	-	(K. T. Kim, Rioux, & Turgeon, 2014)

3 -Bovine pancreatic trypsin
4 - Bovine pancreatic chymotrypsin
5 - Human pancreatic juice collected by fistula
6 - Porcine pepsin
7 - Porcine trypsin
8 – Bovine pre-gastric lipase
9 - Porcine pancreatic lipase
10 - Pancreatic lipase from rat pancreas
11 – Porcine pancreatic lipase
12 – Simulated intestinal juice
13 – Pepsin (unknown source)
14 - Bovine trypsin
15 - Porcine chymotrypsin
16 –Porcine pancreatic α-amylase
17 - α-amylase from human saliva
18 - α-amylase
19 – Porcine pancreatin

Fibre Concentration:
α - 1.25 mg/ml
β- 2.5% by weight
γ - 5% by weight

Material	Description						Reference	Notes
Chitosan	*NAI*	-	-	~81[1] [2,g,η]	-	-	(Espinal-Ruiz, Parada-Alfonso, Restrepo-Sánchez, Narváez-Cuenca, & McClements, 2014)	δ - 0.71 mg/ml ε - 3.43 mg/ml ζ - 0.5 mg/ml η – 0.9% by weight θ - 1.7% by weight ι- 500% w/w compared to substrate κ - 1 mM Λ – 10 mg/ml μ – 2 mg/ml ν - 6.8 - 9.8% w/w depending on the moisture content and bulk density of the fibre. Ξ 0.4% by weight ο – 5 mg/ml π – 13.3 mg/ml
Gum arabic	*NAI*	-	104.1 [h,13,θ]	-	←51.0 [h,14+15,θ]→		(Mouécoucou, et al., 2003)	
	From Acacia tree	-	-	76.2 [M,23,Λ]	-		(O'Connor, Sun, Smith, & Melton, 2003)	
Wheat Bran	Water-insoluble dietary fibre from wheat bran	89.1 [k,18,Λ]	-	-	-	-	(Ou, Kwok, Li, & Fu, 2001)	
	Water-soluble dietary fibre from wheat bran	82.1 [k,18,Λ]	-	-	-	-	(Ou, Kwok, Li, & Fu, 2001)	
	Fibre component of Kellogg's AllBran®	174.5 [k,19,v]	-	-	-	-	(Hardacre, Yap, Lentle, & Monro, 2015)	
	As above	142.2 [l,19,v]	-	-	-	-	(Hardacre, Yap, Lentle, & Monro, 2015)	
Wheat Fibre	'WF600'(J. Rettenmaier & Söhne, Rosenberg, Germany)	115.3 [k,19,v]	-	-	-	-	(Hardacre, Yap, Lentle, & Monro, 2015)	
	As above	105.5 [l,19,v]	-	-	-	-	(Hardacre, Yap, Lentle, & Monro, 2015)	
	'Prolux' (Oppenheimer Pty Ltd., NSW, Australia)	120.4 [k,19,v]	-	-	-	-	(Hardacre, Yap, Lentle, & Monro, 2015)	
	As above	109.0 [l,19,v]	-	-	-	-	(Hardacre, Yap, Lentle,	

							& Monro, 2015)
Resistant Starch	From maize	79.8 [k, 18, Λ]	-	-	-	-	(Ou, Kwok, Li, & Fu, 2001)
Methyl Cellulose	NAI	-	-	~45 [1, 2, g, η]	-	-	(Espinal-Ruiz, Parada-Alfonso, Restrepo-Sánchez, Narváez-Cuenca, & McClements, 2014)
	Carboxymethyl cellulose	80.1 [k, 18, Λ]	-	-	-	-	(Ou, Kwok, Li, & Fu, 2001)
	Carboxymethyl cellulose sodium salt	57.1 [a, 1, α]	74.3 [b, 2, α]	-	88.2 [c, 3, α]	57.7 [c, 4, α]	(K. Ikeda & Kusano, 1983)
	Carboxymethyl cellulose	-	-	93.3 [M, 8, Λ]	-	-	(O'Connor, Sun, Smith, & Melton, 2003)
	NAI	-	-	-	-	-	
Guar gum	NAI	82.6 [k, 18, Λ]	-	-	-	-	(Ou, Kwok, Li, & Fu, 2001)
	NAI	268.5 [k, 19, ν]	-	-	-	-	(Ou, Kwok, Li, & Fu, 2001)
	NAI	229.7 [k, 19, ν]	-	-	-	-	(Ou, Kwok, Li, & Fu, 2001)
Yeast mannan	NAI	77.4 [a, 1, α]	86.5 [b, 2, α]	-	84.9 [c, 3, α]	56.0 [c, 4, α]	(K. Ikeda & Kusano, 1983)
Agar-agar	NAI	80.2 [a, 1, α]	84.0 [b, 2, α]	-	38.3 [c, 3, α]	59.5 [c, 4, α]	(K. Ikeda & Kusano, 1983)
Inulin	NAI	86.7 [a, 1, α]	88.3 [b, 2, α]	-	98.0 [c, 3, α]	66.9 [c, 4, α]	(K. Ikeda & Kusano, 1983)
Xylan	NAI	76.7 [a, 1, α]	82.8 [b, 2, α]	-	23.0 [c, 3, α]	46.5 [c, 4, α]	(K. Ikeda & Kusano, 1983)
	NAI	32.7 [5, γ]	-	31.0 [5, γ]	11.2 [5, γ]	20.0 [5, γ]	(Dunaif & Schneeman, 1981b)
	NAI	-	.	-	← 45.1 [h, 14+15, θ] →		(Mouécouc

							ou, et al., 2003)
Cellulose	Powder 99% pure	78.9 [a, 1, α]	81.1 [b, 2, α]	-	90.6 [c, 3, α]	57.1 [c, 4, α]	(K. Ikeda & Kusano, 1983)
	Solka Floc (Brown Co.)	20.4 [5, γ]	-	4.6 [5, γ]	55.3 [5, γ]	52.9 [5, γ]	(Dunaif & Schneeman, 1981b)
	Alpha-cellulose (Sigma C8002)	67.1 [j, 16, ι]	-	-	-	-	(Dhital, Gidley, & Warren, 2015)
Galacturonic acid	NAI	63.4 [a, 1, α]	90.7 [b, 2, α]	-	78.2 [c, 3, α]	48.5 [c, 4, α]	(K. Ikeda & Kusano, 1983)
Xantham gum	NAI	84.7 [k, 18, Λ]	-	-	-	-	(Ou, Kwok, Li, & Fu, 2001)
Lignin	Sigma	~615 [a, 16, κ]	-	-	-	-	(J. Zhang, Cui, Yin, Sun, & Li, 2013)
	(Lignocel® Type C120, J. Rettenmaier & Söhne, Rosenberg, Germany) with high lignin content	180.9 [k, 19, ν]	-	-	-	-	(Hardacre, Yap, Lentle, & Monro, 2015)
	NAI	124.2 [l, 19, ν]	-	-	-	-	(Hardacre, Yap, Lentle, & Monro, 2015)
	8-54kDa Lignin from Sigma	-	-	155-362.5 [j, 11, μ]	-	-	(J. Zhang, Cui, Yin, Sun, & Li, 2013)
Citrus Unshui	Dietary fibre extract of Citrus Unshui containing arabinose, galactose, xylose and glucose	-	-	47 [j, 11, π]	-	-	(Iwata, Hotta, & Goto, 2012)
Carrageenan	Λ Carrageena	-	-	82.9 [M, 23,	-	-	(O'Connor, Sun, Smith,

	n, type IV			^			& Melton, 2003)
Guluronic acid	NAI	100 [a, 1, α]	81.7 [b, 2, α]	-	99.2 [c, 3, α]	53.9 [c, 4, α]	(K. Ikeda & Kusano, 1983)

Table 2: Dietary fibre and observational risk of small intestinal/pancreatic and liver cancers

Disease/condition	Study design	Comparative statistics (95% CI)	Notes	Reference
Small intestinal cancer	Prospective study of 492,321 individuals with an mean of 7 years of follow-up	Adjusted RR for highest quintile of fibre intake was 0.79 (0.43 – 1.44) vs 1 for lowest.	Carcinoid cancer risk appeared to be increased by increasing intake of fruit and vegetable cancer with fibre from grains associated with a lower total incidence.	(Schatzkin, Park, Leitzmann, Hollenbeck, & Cross, 2008)
Pancreatic cancer	Case-control study with 326 cases of pancreatic cancer	Adjusted OR of 0.4 (0.2-0.7) of highest quintile of fibre intake vs 1 for lowest quintile	Increased intakes of both soluble and insoluble fibre were linked a significantly reduced OR	(Bidoli, Pelucchi, Zucchetto, Negri, Dal maso, Polesel, et al., 2012)
	Case-control study with 384 cases of pancreatic cancer	Adjusted OR of 0.57 (0.37-0.86) and 0.56 (0.37 – 0.84) for highest quintile of frequency of fruit and vegetable consumption and vs 1 for lowest quintile	Insoluble fibre consumption also significantly associated with reduced OR of pancreatic cancer risk. Potential for diet-gene interaction also noted.	(Jansen, Robinson, Stolzenberg-Solomon, Bamlet, De Andrade, Oberg, et al., 2011; Jansen, Robinson, Stolzenberg-Solomon, Bamlet, Tan, Cunningham, et al., 2013)
	Case-control study with 532 cases of pancreatic cancer	Adjusted OR of 0.60 (0.31-1.2) for ≥2 servings of whole grains/day versus 1 for <1 serving/day	Frequency of consumption of brown rice and tortillas was negatively associated with OR while frequency of	(Chan, Wang, & Holly, 2007)

			oatmeal/oat bran were positively associated with OR.	
	Case-control study with 186 cases of pancreatic cancer	Adjusted OR of 0.52 (0.21–1.30) for highest quartile of fibre intake versus 1 for lowest	No significant trend also noted for association of frequency of fruit and vegetable consumption and OR	(J. Zhang, Dhakal, Gross, Lang, Kadlubar, Harnack, et al., 2009)
Hepatic cancer	Case-control, multicentre study with 185 cases of hepatocellular carcinoma	Adjusted OR of 0.72 (0.31–1.64) for top quartiles of vegetables and 0.48 (0.22–1.05) for fruit consumption vs 1 for lowest quartile	-	(Talamini, Polesel, Montella, Dal Maso, Crispo, Tommasi, et al., 2006)
	Prospective multicentre study of 477,206 individuals with a mean follow-up of 11.4 years	HR of 0.51 (0.31–0.83) for highest quartile of fibre intake vs 1 for lowest quartile	Adjusted HR of 0.59 (0.37–0.95) per 10 g of fibre consumed daily suggested. No association between fibre intake and biliary tract cancer evidenced.	(Fedirko, Lukanova, Bamia, Trichopolou, Trepo, Nöthlings, et al., 2013)

HR = Hazard Ratio, OR = Odds ratio, RR = relative risk. Data searches were carried out using www.scopus.com and focused on publications from 2000 onwards.

Table 3: Summary of associative studies linking dietary fibre intake and observational risk of selected pancreatic and hepatic/biliary tract disease

Disease/condition	Study design	Comparative statistics (95% CI)	Notes	Reference
Pancreatitis	A prospective study with 36,436 women, aged over 65 years in cases of acute and chronic pancreatitis	Adjusted OR of 0.98 (0.72-1.33 - acute) 1.67 (0.87-3.21 - chronic) for the highest quartile of crude fibre intake vs 1 for the lowest and 0.97 (0.74-1.26 - acute) and 0.96 (0.57-1.60 - chronic) for the highest tertile of fruit and vegetable intake frequency vs 1 for the lowest.		(Prizment, Jensen, Hopper, Virnig, & Anderson, 2015)
Non-alcoholic fatty liver disease	Observational study in 63 obese patients	Markers of non-alcoholic fatty liver disease were not associated with dietary fibre intake across different classifications of obesity.		(Ricci, et al., 2011)
Gall bladder removal	A prospective study with 69,778 women aged 35 to 61 over 16 years of follow-up	Adjusted RR of 0.87 (0.78-0.96) for highest quintile of intake vs 1 for lowest.	Every 5 g of fibre consumed led to a significant reduction of RR (0.94, 95% CI 0.92-0.98) of gall bladder removal and insoluble fibre appeared to be particularly associated with reduced RR	(Tsai, Leitzmann, Willett, & Giovannucci, 2004)

OR = Odds ratio, RR = relative risk. Data searches were carried out using www.scopus.com and focused on publications from 2000 onwards.

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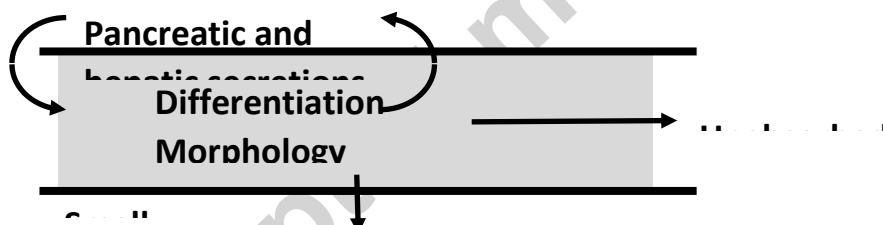
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Graphical abstract [Separate file]

Pancreatic and
hepatic secretions

Differentiation
Morphology

Undisturbed

Small

Absorption

Highlights [3 to 5 bullet points. Separate file]

- Dietary fibres impact on small intestinal motility and digestion rates.
- Different dietary fibres can also affect the exocrine secretions of the pancreas and liver.
- These effects are likely to have consequences on long-term health if fibre is consumed habitually, although limited evidence from intervention studies supports this hypothesis.
- There is limited evidence evaluating the association of dietary fibre or fibre-containing plant foods with diseases of the small intestine, liver and exocrine pancreas.