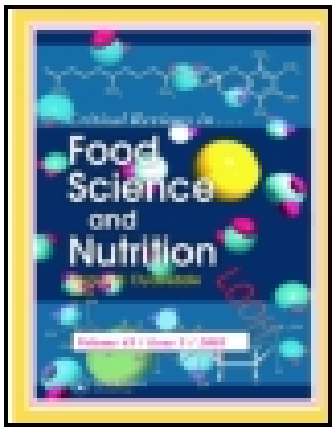


Critical Reviews in Food Science and Nutrition
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/bfsn20

# The role of alginates in regulation of food intake and glycemia: a gastroenterological perspective

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Accepted author version posted online: 11 Oct 2013.

# The role of alginates in regulation of food intake and glycemia: a gastroenterological perspective

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*Received: / Accepted: / Published:*

**Abstract**

Regulation of food intake through modulation of gastrointestinal responses to ingested foods is an ever-growing component of the therapeutic approaches targeting the obesity epidemic. Alginates, viscous and gel-forming soluble fibers isolated from the cell wall of brown seaweeds and some bacteria, are recently receiving considerable attention because of their potential role in satiation, satiety and food intake regulation in the short-term. Enhancement of gastric distension, delay of gastric emptying and attenuation of postprandial glucose responses may constitute the basis of their physiological benefits. Offering physical, chemical, sensorial and physiological advantages over other viscous and gel-forming fibers, alginates constitute promising functional food ingredients for the food industry. Therefore, the current review explores the role of alginates in food intake and glycemic regulation, their underlying modes of action and their potential in food applications.

**Keywords: Fiber; viscous; gelling; satiety; glucose; obesity**



 

## A. Introduction

Obesity has reached global epidemic proportions, with more than one billion adults affected by this chronic disorder, and is a major contributor to the global burden of chronic disease and disability (Fujioka, 2002). Etiologically, the interaction of a permissive environment of serious social and psychological dimensions, characterized by a sedentary lifestyle as well as excessive intake of high energy-density foods and beverages, with genetic polymorphisms provides a partial explanation of the onset of obesity (Fujioka, 2002; Rosas-Vargas, et al., 2011). Failure of multidisciplinary therapeutic approaches to target the obesity epidemic has been attributed mainly to the inability of individuals to control their food intake (Rosas-Vargas, et al., 2011).

The regulation of short- and long-term food intake occurs through complex physiological mechanisms, involving a wide variety of molecules interacting through diverse biochemical circuits (Anderson, et al., 2006; Rosas-Vargas, et al., 2011). Many of the signals that regulate food intake in the short-term, including blood glucose, are activated by gastrointestinal responses to food ingestion (Anderson, et al., 2006). These include stomach distension, gastric emptying, gut motility and gastrointestinal peptides (Delzenne, et al., 2010; Phillips and Powley, 1996).

Many factors are believed to affect gastric distension and emptying, including the volume and energy density of a meal as well as its viscosity and particle size (Horowitz, et al., 1994). Because increased gastric distension and slower gastric emptying rates are associated with decreased food intake, there has been increased interest in maximizing and prolonging gastric distension and emptying in order to control energy intake. This has led to the emergence of

products capable of optimizing gastric volume cues, especially those rich in bulking agents with strong gelation properties including the polysaccharide fibers guar gum, pectins and alginates (Birketvedt, et al., 2005). Considerable research has shown that the addition of guar gum and pectins to liquids or solids contribute to a reduction in food intake (Wanders, et al., 2011). The role of alginate in food intake and body weight management has generated significant research interest in addition to being an attractive industrial ingredient in food applications for gelling, viscosifying and stabilizing purposes. Alginates, a group of polyuronic saccharides, are gelling fibers isolated from the cell wall of various brown seaweeds and some bacteria (Brownlee, et al., 2005). Since alginate forms gels mainly upon entering the acidic gastric environment (Hoad, et al., 2004) rather than in the product matrix, it is not burdened with the same palatability problem as other viscous fibers. In addition, unlike other viscous fibers, alginate has the capacity to withstand moderate amounts of thermal stress as might be encountered during boiling or cooking of the product (Draget, 2009).

The objective of the current review is to reveal the potential applications of alginates in foods for the purpose of energy intake and glycemic regulation, with special emphasis on sodium alginate as the most commonly used form in food applications. Therefore, in the following, a background review on energy intake control is provided first, comprising a description of the role of postprandial glycemic responses as determinants of short-term appetite. Glycemic regulation is briefly addressed in this review because it was proposed as one of the components of food intake regulation system and due to its significance in the therapeutic management of type 2 diabetes. This is followed by an in-depth examination of alginates as potential additives to foods for the modulation of food intake and metabolic regulation.

## B. Physiology of Food Intake Regulation

The regulation of food intake is a complex process, which involves the interaction of food with physiological targets in the short term and comprises an adaptive response to energy metabolism in the long term (Delzenne, et al., 2010). Our understanding of factors that regulate food intake is rapidly growing, with the continuous discovery of novel molecules that may influence the ingestive behavior (Capasso and Izzo, 2008). Food intake regulation relies on a balance between hunger, satiation and satiety (Janssen, et al., 2011). The identification of the biochemical basis for hunger and satiety and of all signals controlling these neurobiological processes has been the subject of extensive debate (Chaput and Tremblay, 2009). It is agreed that these sensations are the result of complex interactions between central nervous system circuits and peripheral signals, which mainly originate from the gastrointestinal tract (Stubbs, 1999), liver (Stubbs, 1999) and adipose tissue (Ahima, 2006).

Reduction of energy intake can be achieved in one of the two non-mutually exclusive ways, including earlier satiation and/or prolongation or enhancement of satiety (Mattes, et al., 2005). Satiation refers to processes that promote meal termination and thus limit meal size (Camilleri and Grudell, 2007). Satiation might evoke various postprandial feelings, including pleasure, distress, fullness, nausea or bloating (Camilleri, 2006). On the other hand, satiety refers to postprandial events that affect the interval to the next meal and thus regulate meal frequency (Camilleri and Grudell, 2007). Hence, acute intake can be modulated either by bringing feeding to an end sooner and limiting energy consumed at that meal and/or by increasing inter-meal interval and reducing the number or size of eating episodes following that meal (Mattes, et al., 2005).

Alginates, as viscous and gel-forming fibers, exert their actions on food intake regulation through the gut, primarily the stomach. The gut influences feeding behavior by generating hunger, satiation and satiety signals secondary to acute changes in mechanical and chemical stimuli (Cummings and Overduin, 2007; Naslund and Hellstrom, 2007; Ritter, 2004). Stomach is one of the important components of the gastrointestinal tract having a significant role in the regulation of both satiation and satiety (Wisen and Hellstrom, 1995). The role of gastrointestinal tract in energy intake control is further elaborated in the following sections.



## 1. Gastrointestinal tract and food intake regulation

Upon contact with ingested food, the gut senses meal volume and nutrient composition and initiates a series of homeostatic mechanisms linking the gut to the brain axis for the regulation of energy intake (Das, 2010). Although the exact mechanism by which communication occurs is still not clear, a group of incretins and other gut-derived hormones are suggested to be involved (Matzinger, et al., 2000), which consequently modulate the secretion and actions of various hypothalamic neurotransmitters and peptides (Chaudhri, et al., 2006). Indeed, the gastrointestinal tract releases more than 20 different regulatory peptide hormones that have been reported to influence various physiological processes in food intake regulation system.

Responses of the gastrointestinal tract to ingestion of food are divided into three phases including cephalic, gastric and intestinal (Capasso and Izzo, 2008). The cephalic phase (pre-ingestion phase) includes the auditory, cognitive, visual and olfactory stimuli induced by the meal. Sight, smell and taste of a food activate the parasympathetic outflow, which triggers both secretor and motor events in the proximal and distal gastrointestinal tract in order to prepare the system to receive food (Cuomo and Sarnelli, 2004). The gastric phase involves a highly complex

multi-compartmental process. It includes stomach accommodation to a meal, preventing any increase in intragastric pressure that would result in a feeling of discomfort (Camilleri, 2006). Accommodation comprises relaxation of the proximal stomach by activation of inhibitory neurons of the gastric wall. Finally, the intestinal (post-ingestion) phase involves duodenal, intestinal and colonic responses to food emptying from the stomach (Xing and Chen, 2004).

While satiation signals arise primarily from stomach mechanical distension in response to the physical characteristics of food, satiety signals are largely dependent on the chemical effects of food in the intestine. The stomach wall encloses mechanoreceptors, which are neural sensors of tension, stretch and volume (Park and Camilleri, 2005). Output from these mechanoreceptors is sent to the brain by vagal and spinal sensory nerves, using a complex array of neurotransmitters (Cummings and Overduin, 2007). On the other hand, a number of gut peptides, secreted from enteroendocrine cells in response to food ingestion, mediate intestinal satiety including cholecystokinin (CCK), glucagon-like peptide 1 (GLP-1), oxyntomodulin, peptide YY (PYY), apolipoprotein A-IV and ghrelin (Capasso and Izzo, 2008). These messengers may diffuse through interstitial fluids to activate nearby extrinsic sensory fibers and/or enter the bloodstream to function as hormones (Cummings and Overduin, 2007; Park and Camilleri, 2005). Once in the bloodstream, some peptides have direct access to the arcuate nucleus of the hypothalamus and to the area postrema, brain regions involved in the regulation of food intake, whereas others can influence the activity of vagal neurons which in turn project into these brain areas (Stanley, et al., 2004). Intestinal satiety signals are short-lasting, but can interact with adiposity hormones such as insulin and leptin and hence relay signals involved in long-term body weight regulation (Cummings and Overduin, 2007).

Gastrointestinal motility strongly influences food intake behaviors through regulation of satiation and satiety signals. Altered gastrointestinal motility has been described in obese as well as in anorexic individuals, suggesting a role of gut motility in the development of changed eating behaviors (Xing and Chen, 2004; Zipfel, et al., 2006). Indeed, a relationship between gastric motility-linked parameters such as gastric distension and gastric emptying and appetite-related measures including hunger and fullness has been well-established (Feinle, et al., 2001; Hveem, et al., 1996).



**a. Gastrointestinal distension, satiation and satiety**

Stomach distension plays an essential role in the regulation of hunger, satiation and satiety. Alterations in total gastric volumes have been estimated to explain 50-60% of the variance in fullness ratings when measured both in obese and non-obese individuals (Cecil, et al., 1999; Rolls and Roe, 2002). Early work reported that hunger ratings and meal intake decreased when a gastric balloon was inflated to a volume of 400 mL or more (Geliebter, et al., 1988). Both proximal and distal stomach areas have comparable mechanosensitivity and were described as important contributors to satiation and satiety (Lee, et al., 2004). When balloons were placed in the proximal stomach, decreased hunger feelings and increased fullness sensations were described in healthy and severely obese individuals (Feinle, et al., 2002; Rigaud, et al., 1995). However, associations with lower energy intake were not found suggesting a role of proximal stomach in generating satiation rather than satiety signals. In support of a role of distal stomach filling in satiation and satiety, ultrasound and scintigraphy measurements showed a direct correlation of antral volume and distension with the sensations of hunger and fullness from one

 

side and with the amount of ingested liquid or solid foods from another side in healthy individuals (Sturm, et al., 2004).

Gastric distension triggers stretch and tension mechanosensitive receptors, which in turn relay information to the hindbrain and other brain areas involved in food intake regulation via vagal and splanchnic nerves (Grundy, 2002; Phillips and Powley, 2000). Vagal afferent neurons that detect gastric distension play an important role in the process of satiation (Ritter, 2004). However, under normal conditions, gastric distension does not occur in the absence of postgastric signals (van de Wall, et al., 2005). Gastric distension, intestinal nutrients and gut hormones interactively contribute to vagal afferent activation. For instance, CCK enhances the satiating effect of gastric distension (Kissileff, et al., 2003) by further sensitizing gastric and duodenal mechanosensitive vagal afferents (Davison and Clarke, 1988; Ewart and Wingate, 1983). Gastric distension and CCK cooperatively reduce food intake in a variety of species including rats, monkeys and humans (Kissileff, et al., 2003; Lal, et al., 2004; McHugh and Moran, 1986; Schwartz, et al., 1991). In addition, neurons containing GLP-1 in the nucleus of the solitary tract were activated by gastric distension within the physiological range (Vrang, et al., 2003).

In contrast to mechanosensation, nutrient sensation is less likely to play a role in regulation of satiation upon food presence in the stomach. In rats equipped with inflatable cuffs around the pylorus preventing content from leaving the stomach, infusion of a non-nutritive saline solution or of a nutrient solution equally decreased food intake in a volumetrically proportionate manner (Phillips and Powley, 1996; Powley and Phillips, 2004). In humans, postprandial gastric volumes strongly correlated with postprandial sensations of hunger and satiation irrespective of nutrient

composition (Goetze, et al., 2007). Thus, stomach does not meaningfully detect the nutrient or caloric composition of a meal while the intestine, which is a major regulator of gastric emptying, does (Cummings and Overduin, 2007). Gastric emptying is an important contributor to the satiety state that lasts for several hours after a meal.

**b. Gastrointestinal emptying and satiety**

As the stomach gradually empties its contents into the small intestine, the contribution of gastric distension to satiation and satiety regulation gradually decreases but remains present. The emphasis shifts towards intestinal exposure to nutrients and gastric emptying rate in the regulation of satiety mechanisms, although not entirely. In fact, nutrient gastric emptying represents an interaction between gastric volume and nutrient-induced duodenal feedback. Under normal conditions, sufficient nutrient emptying must occur in order to increase the magnitude of duodenal feedback to withhold a given gastric volume (Moran, et al., 1999). The association between gastric emptying and satiety is complex, but several studies confirm that this is an inverse relationship (Carbonnel, et al., 1994; Doran, et al., 1998; Spiegel, et al., 2000). Significant negative correlations were described between ratings of postprandial hunger and the time needed for 90% of the meal to empty (Sepple and Read, 1989). Physiologically- or artificially-induced delay in gastric emptying was found to be linked with increased feelings of satiety and fullness (Di Lorenzo, et al., 1988; Wisen and Hellstrom, 1995). Combined ultrasound and scintigraphy studies also described inverse associations between gastric emptying rates and feelings of satiety in healthy participants (Hveem, et al., 1996; Jones, et al., 1997).

Feedback received from the intestine in response to nutrient exposure influences gastric emptying. Sensation of intestinal contents is mainly based on mucosal recognition of luminal

osmolarity, viscosity and nutrient digestion products and on mucosal mechanical stimulation to a lesser extent (Cummings and Overduin, 2007; Woods, 2004). Consequently, satiety-regulating hormones are released, exerting their action either directly on the hypothalamic arcuate nucleus via the blood-brain barrier or indirectly via the vagus nerve as previously discussed. In addition, the larger intragastric volume and hence the greater gastric distension resulting from delayed gastric emptying may also explain the increased feelings of satiety and the delayed return of hunger sensations (Geliebter, 1988; Wisen and Hellstrom, 1995).



## 2. Glycemia and hunger control

Among satiety signals whose release is directly shaped by gastric measures such as gastric distension and gastric emptying is blood glucose. Glycemic responses to foods have been proposed as one of the regulators of food intake. The glucostatic theory, formalized by Jean Mayer in the mid 1950s, postulated that reduced glucose utilization via glucoreceptors in critical brain regions including the hypothalamus leads to perceptions of hunger (Mayer, 1953; Mayer, 1955). Decreased glucose utilization by metabolizing cells was considered a signal for meal initiation. More precisely, a role of glucose dynamics and oscillations in glucose levels rather than of absolute blood glucose values was emphasized as more important in the control of meal initiation and termination of food intake (Bray, 1996). A fall in blood glucose was correlated with meal initiation in rats (Campfield and Smith, 1986; Campfield and Smith, 1990; Louis-Sylvestre and Le Magnen, 1980). Blood glucose concentrations decline by 6-8% before meal onset both in the dark and light phases of their light-dark cycle (Louis-Sylvestre and Le Magnen, 1980). Similar results were found in human studies, in which both the initiation of meals and the perception of hunger were synchronized with transient blood glucose declines (Campfield, et al.,

1996; Melanson, et al., 1999; Melanson, et al., 1999). In addition, inverse associations of subjective hunger and food intake with blood glucose concentrations following a meal were also reported (Anderson, et al., 2002). However, evidence is still not consistent and sufficient to establish blood glucose, whether acute or sustained, as a primary determinant of satiety and food intake in humans. Various studies found no associations between blood glucose and satiety when circulating glucose concentrations were raised intravenously (Lavin, et al., 1996) and between glucose postprandial responses and subsequent food intake (Krishnamachar and Mickelsen, 1987; Stewart, et al., 1997). Furthermore, several factors such as insulin and incretin hormones co-vary with postprandial glycemic concentrations, making it difficult to determine whether blood glucose per se or the associated factors are responsible for short-term regulation of satiety and food intake (Holt, et al., 1996; Raben, et al., 1996).

Understanding the effects of food attributes on the digesta and hence on the dynamics of gastric distension and gastric emptying is crucial for a better evaluation of the role of these attributes in food intake and glycemic regulation. Assessing the effects of digesta characteristics on gastric action is rendered complex by many factors, including physical and chemical properties of the digesta (Powley and Phillips, 2004), ongoing dilution with gastric secretions (Marciani, et al., 2001), interaction among various nutrients (Sakaguchi, et al., 1994) as well as feedback regulation via gastro-entero-pancreatic hormones (McTigue and Rogers, 1995; Schirra, et al., 2000) and components of the autonomic nervous system (Lefebvre, et al., 2005). Moreover, the current methods used to define the effect of physical factors on intragastric processing of food have many limitations. For instance, gamma scintigraphy, clinically used to evaluate gastric emptying, provides information only about the amount of meal remaining in the stomach rather

than the total gastric volume including secretions (Chaudhury, 1974). Moreover, ultrasound cannot measure accurately volumes in the stomach body and fundus because of air-fluid interfaces that disrupt ultrasound beam (Marciani, et al., 2001). In addition, the atypical positioning of the subject that is needed for external measuring devices such as magnetic resonance imaging (MRI) may also affect the accurate quantitative evaluation of these interactions (Kwiatek, et al., 2006).



### 3. Food determinants of gastric distension and emptying

While increased meal volume and the presence of viscous gel-forming fibers such as alginates strongly promote stomach distension, other components of the meal interact to profoundly alter gastric emptying rate. In addition to the consistency of food and to its caloric content, volume, acidity, osmolarity and viscosity of the meal strongly influence gastric emptying (Burks, et al., 1985; Macdonald, 1996). Voluminous meals accelerate gastric emptying rate, whereas solutions of high osmolarity slow it (Anderson, et al., 2006). The mechanical functions of gastric emptying also depend on food consistency. While liquid meals empty without a lag phase, solid meals empty in a biphasic manner thereby prolonging gastric emptying (Hellstrom, et al., 2006). Moreover, gastric emptying speed is inversely correlated to the caloric concentration of a meal (Calbet and MacLean, 1997). Although meal caloric content and viscosity are two major independent factors controlling gastric emptying, they were found to have an additive effect in delaying gastric emptying in healthy individuals (Marciani, et al., 2001). However, nutrient content was proven to be a stronger determinant of gastric emptying than viscosity itself. The presence of nutrients in a high viscosity meal had a more powerful effect on slowing gastric emptying with respect to a non-nutrient meal of equal initial viscosity.

Knowing that gastric emptying is strongly influenced by pyloric contractions, meal nutrients may have induced pylorospasm as it was reported with intraduodenal lipid infusion (Heddle, et al., 1989).

Amongst food properties, viscosity impacts gastrointestinal functions. Viscosity is usually discussed in the context of soluble dietary fibers such as alginates. A role of viscosity in the regulation of gastric distension and emptying has been demonstrated. Increased viscosity of the meal and of gastric contents is known to promote increases in antral volumes and expansion of the stomach (Marciani, et al., 2001; Prove and Ehrlein, 1982). By absorbing large quantities of water and forming gels, viscous fibers reduce the amplitude of antral contractions, which normally function to decrease antral volumes, and hence promote total gastric distension. On the other hand, the role of viscosity per se as a regulator of gastric emptying remains unclear. Several animal (Cherbut, et al., 1990; Prove and Ehrlein, 1982) and human (Marciani, et al., 2000; Sandhu, et al., 1987; Wilmshurst and Crawley, 1980) studies have shown that meal viscosity influences gastric motor function and delays consequently gastric emptying. For instance, in healthy volunteers, increasing the viscosity of rice pudding by addition of locust bean gum significantly lowered the rate of gastric emptying (Darwiche, et al., 2003). However, these studies did not assess viscosity levels in the stomach and small intestine. In fact, not only the inherent meal viscosity but also the viscosity of the resultant digesta in the gut is an important determinant of gastric emptying (Guerin, et al., 2001). Evaluating the viscosity of fluid digesta is a complex and difficult task, mainly because of the concentration and size of undigested particles in the sample (Dikeman and Fahey, 2006). In the study of Marciani (Marciani, et al., 2000), despite the fact that initial meal viscosity varied 1000-fold, emptying

rates differed by a factor of only 1.3. In response to higher viscosity meals, volume of gastric secretions for meal dilution is increased beyond basal acid output, causing a reduction of digesta viscosity and consequently a minimal delay in gastric emptying (Marciani, et al., 2000). It should be noted that such enhanced stomach secretions may also play a role in increasing gastric volumes in response to increased meal viscosity (Marciani, et al., 2001). By regulating both gastric distension and gastric emptying, meals with increased viscosity, especially those with added viscous fibers, strongly contribute to sensations of satiation and satiety (Bergmann, et al., 1992; Di Lorenzo, et al., 1988; Mattes and Rothacker, 2001; Zijlstra, et al., 2008).



Increasing the viscosity of meals and utilizing food components that promote the formation of gels within the stomach (Hoad, et al., 2004; Marciani, et al., 2000) have been suggested as one of the routes towards enhancing satiation and satiety feelings, suppressing energy intake and attenuating glycemic responses via the processes of increased gastric distension and/or delayed gastric emptying (Bergmann, et al., 1992; Di Lorenzo, et al., 1988). Among nutrients that can increase meal viscosity, dietary fibers have the most documented effects on gastric functions, satiety, food intake and glycemia. Considering all physico-chemical properties of fibers, viscosity was found to explain reductions in subjective hunger sensations and in short term energy intake to a greater extent than solubility or fermentability in the systematic review of Wanders (Wanders, et al., 2011). The physiological importance of viscosity alterations of gut digesta in response to the consumption of viscous fibers such as alginates has been well documented.

### C. Role of Fibers in Food Intake and Glycemic Regulation: Importance of Viscosity

Scientific and regulatory bodies around the world have faced various challenges to achieve an internationally acceptable definition for dietary fiber by Codex (Phillips and Cui, 2011). In addition to addressing the biological, chemical and nutritional characteristics of dietary fibers, recent regulatory requirements have urged the need for analytical definitions.

Dietary fibers can be classified according to chemical, physical or physiological criteria (Cummings, et al., 1997; Englyst and Englyst, 2005). Fibers are most commonly characterized based on their solubility. Distinction between soluble and insoluble dietary fibers is based on the solubility of dietary fiber in hot aqueous buffer solutions (Sullivan and Carpenter, 1993). Insoluble fibers primarily consist of cellulose and some hemicelluloses, resistant starch and chitin while soluble fibers include pectins, beta (β)-glucans, galactomannan gums, mucilages and some hemicelluloses. Used as a means to broadly characterize the physiological effects of fibers, solubility per se is not the best indicator. Unlike soluble non-viscous fibers, soluble viscous fibers associate with improvements in blood glucose and lipid concentrations, prolonged gastric emptying and slower transit time through the small intestine (Wong, et al., 2006). In randomized controlled trials, soluble viscous fibers comprising pectins, gums and mucilages were shown to be more effective in improving lipid profile and glycemia in healthy individuals when compared to insoluble fibers including hemicelluose, cellulose and lignins (Aller, et al., 2004). In addition, a superiority of soluble viscous fibers such as guar gum or psyllium in improving insulin sensitivity was reported in comparison to insoluble cellulose in short-term studies on animal models (Cameron-Smith, et al., 1997; Song, et al., 2000). Accordingly, viscosity has been recognized as an important physico-chemical property of dietary fibers linked to various beneficial physiological responses.

## 1. Characterization of viscous dietary fibers

A number of definitions and terms are used to describe viscosity (Dikeman and Fahey, 2006). Viscosity is basically defined as the proportional relationship between the flow of a fluid obeying Newton's law and the force directed on that fluid. For dietary fibers, viscosity is used to describe the ability of some polysaccharides to thicken or form gels when mixed with fluids (Guillon and Champ, 2003). It results from physical entanglements among the polysaccharide constituents within the fluid. Apparent viscosity is the most common term used when describing dietary fibers, since most fiber solutions are pseudoplastic in nature and deviate from Newtonian flow behavior (McDonald, et al., 2001). It is defined as the viscosity of a non-Newtonian fluid at a specified shear rate. Viscous dietary fibers include many soluble polysaccharides such as gums, pectins, galactomannans, β-glucans and alginates (Roberfroid, 1993). Various physico-chemical characteristics of dietary fibers, such as structure, chemical composition, dose and molecular weight, determine their ability to form viscous solutions (Dikeman and Fahey, 2006; Dikeman, et al., 2006).

Both structure and chemical composition of dietary fibers influence their hydration rate as well as the extent to which their resultant viscosity is affected by pH in the gastrointestinal tract. Viscosity of dietary fibers in solution strongly depends on their hydration rate. Some fibrous preparations hydrate so slowly that they attain only 60% of their maximum viscosity even after 5 hours (Ellis and Morris, 1991). The viscosity of three preload drinks rich in glucomannan, cellulose or a new viscous polysaccharide were equally low immediately after mixing, but gradually increased over a period of 75 minutes (Vuksan, et al., 2009). The degree to which viscosity of the gastrointestinal content is affected by pH is another important factor to consider



 

(Kristensen and Jensen, 2011). This highly depends on the source of dietary fibers and their proportion of neutral to acidic residues. Dietary fibers are exposed to extreme variations in pH upon transit throughout the gastrointestinal tract. Acidification results in the release of non-starch polysaccharides at first, followed by the breakdown of these polysaccharides (Dikeman and Fahey, 2006). Viscosity of guar gum preparations is generally unaffected (Brownlee, et al., 2005) or reduced (Bobboi and Stephens, 1996) upon acidification, whereas acidification induces numerical increases in viscosity of solutions of xanthan gum and some alginates (Dikeman and Fahey, 2006). On the other hand, dose and molecular weight of polysaccharides have a positive non-linear effect on viscosity of solutions at a constant temperature. In pigs, jejunal digesta viscosity was strongly dependent on dietary guar gum levels (Ellis, et al., 1995), and high and medium molecular weight guar gum flours resulted in greater solution and digesta viscosities compared with controls of lower molecular weights (Roberts, et al., 1989).

Viscous dietary fibers have been always considered as first-class candidates for addressing various aspects of satiation, satiety and energy intake control as well as of glycemic regulation.

## 2. Viscous dietary fibers and food intake regulation

In general, dietary fibers are described to have greater satiating properties compared with digestible polysaccharides and simple sugars (Howarth, et al., 2001; Pereira and Ludwig, 2001). However, these outcomes vary according to the physico-chemical properties (viscosity, solubility and fermentability) of fibers. By interacting with the stomach and intestine, viscous and gel-forming fibers, including alginates, have the most significant effects on stomach distension,

prolongation of gastric emptying, hindering of nutrient digestion and absorption and consequently modulation of the release of appetite hormones (Wanders, et al., 2011).

Very few studies have described dietary fibers in terms of their physico-chemical characteristics including molecular weight, fermentability and viscosity, when studying their satiating potentials (Kristensen and Jensen, 2011). Increased viscosity of a liquid meal with psyllium (Bergmann, et al., 1992) and locust bean gum (Marciani, et al., 2001) enhanced satiety levels in healthy volunteers, irrespective of whether the beverage contained other nutrients. When comparing wheat bran, oat bran and guar gum beverages to a control beverage in healthy adults in terms of their impacts on satiety, only the guar gum beverage with a 50- to 700-fold higher viscosity at time of ingestion in comparison to wheat and oat bran beverages increased satiety as compared to the control beverage (Lyly, et al., 2009). In adolescents, new viscous polysaccharide (a highly viscous fiber manufactured from a mixture of xanthan, glucomannan and sodium alginate) beverage suppressed food intake at the next meal relative to both glucomannan and cellulose beverages even though beverages were identical in volume, caloric content and taste (Vuksan, et al., 2009).

The satiating properties of viscous dietary fibers have been explained by various mechanisms, all of which are related to several stages in the process of appetite regulation such as taste, gastric emptying, absorption and fermentation (Burton-Freeman, 2000). The role of colonic fermentation of fibers, more precisely fermentation products short-chain fatty acids, in appetite regulation is addressed in the following.

**a. Short-chain fatty acids and satiety regulation**

Anaerobic fermentation of dietary fibers by colonic microbiota is the major source for the production of short-chain fatty acids (Al-Lahham, et al., 2010). Around 80% of the short-chain fatty acids present in human colonic lumen include acetate, propionate and butyrate (Cummings, et al., 1987). About 90% of these short-chain fatty acids are absorbed into the colon; while butyrate is almost entirely used by the colonocytes as energy substrates (Roediger, 1980), propionate is primarily removed by the liver (Cummings, et al., 1987). Acetate, on the other hand, passes freely into peripheral circulation (Hong, et al., 2005). Short-chain fatty acids were found to be strongly implicated in various biological functions related to host health. They have been recently proposed as key signaling molecules in satiety regulation and energy homeostasis.

There is increasing evidence attributing the satiating properties of fermentable dietary fibers to their major fermentation products, short-chain fatty acids. While in ruminants a substantial amount of evidence showed that absorbed propionic acid causes satiety and reduces food intake (Anil and Forbes, 1980; Bradford and Allen, 2007), only two studies in humans demonstrated that dietary supplementation of propionic acid induces satiety (Liljeberg, et al., 1995; Ruijschop, et al., 2008). Although under debate, various mechanisms of action, integrating neuronal, endocrine, paracrine and autocrine pathways, were suggested. Short-chain fatty acids play a role in slowing gastrointestinal motility, thus controlling digestion and nutrient absorption and eliciting an anorexigenic effect. Although the majority of the studies linking short-chain fatty acids to gastrointestinal motility stems from ruminant studies (Kendall and McLeay, 1996), some studies on non-ruminants revealed that short-chain fatty acids may regulate the overall transit time of the digesta through the large intestine (Dass, et al., 2007; Tazoe, et al., 2008). Such responses were hypothesized to occur via three possible pathways: 1) a direct effect of short-



 

chain fatty acids on intestinal smooth muscle tone; 2) short-chain fatty acid stimulation of the vagal nerves in the gut; and 3) as an indirect consequence of short-chain fatty acid-induced secretion of PYY and other regulatory peptides known to play a role in gastrointestinal motility (Cherbut, 1995). Furthermore, by modulating the release of various appetite-related hormones including PYY, ghrelin and leptin, short-chain fatty acids were suggested to regulate appetite (Dumoulin, et al., 1998). For instance, direct infusion of short-chain fatty acids into rabbit colons increased PYY secretions through direct interaction with PYY cells (Longo, et al., 1991). Feeding rats a diet supplemented with the fermentable inulin over 3 weeks reduced ghrelin levels in comparison to a standard diet (Delzenne, et al., 2005). In addition, propionic acid was shown to induce the production of the satiety hormone leptin by human, mouse and ruminant adipose tissue (Al-Lahham, et al., 2010).



### 3. Viscous dietary fibers and glycemic regulation

In addition to regulating food intake, viscous and gel-forming fibers including alginates play a significant role in glycemic control. While insoluble fibers such as wheat bran have little effect on glycemia, meals containing soluble viscous fibers result in considerable reductions in postprandial glucose responses (Hallfrisch, et al., 2000; Ohta, et al., 1997). These beneficial physiological impacts of viscous fibers have been reported in various species, including dogs, rats and humans. In canines, high viscosity 5% glucose solutions significantly reduced maximum blood glucose concentrations in reference to other glucose solutions with lower degrees of viscosity (Reppas and Dressman, 1992). In rats fed guar gum diets, the increase in digesta viscosity was strongly associated with reductions in glycated hemoglobin (Gallaher and

Schaubert, 1990). Similarly, in humans, 79-96% of the reduction in postprandial plasma glucose was attributed to the increased viscosity of oat gum meals (Wood, et al., 1994).

Several events may explain the reductions in plasma glucose concentrations in response to consumption of viscous fiber sources. A delay in gastric emptying through formation of a thick gel matrix in the gut may provide a partial explanation. Some studies support the reduction in glycemic responses following the consumption of viscous polysaccharides via slower gastric emptying and small intestinal transit time (Wursch and Pi-Sunyer, 1997). However, reduction in gastric emptying alone is not the sole mechanism explaining altered glycemic responses to viscous fiber ingestion. In healthy volunteers, guar gum added to 50 g glucose test drinks at doses of 2.5 g or 14.5 g successfully lowered postprandial plasma glucose, without altering gastric emptying (Jarjis, et al., 1984). In addition to gastric responses, beneficial impacts of viscous polysaccharide ingestion on glucose absorption in the small intestine have been also noted. By these fibers entering the small intestine, their resultant gel matrix can thicken intestinal contents, reducing hence the contact between food and digestive enzymes and decreasing the diffusion of nutrients including glucose for absorption (Eastwood and Morris, 1992; Malkki, 2001). The absorption rates of carbohydrate, protein and fat decreased linearly with increased concentrations of guar gum in the jejunal perfusate of miniature pigs (Ehrlein and Stockmann, 1998). However, the lowered digesta viscosity upon arrival to duodenum due to dilution by gastric secretions in the stomach, as previously indicated, suggests a more important relative contribution of delayed gastric emptying than increased intestinal viscosity in attenuating postprandial glucose responses to viscous fibers. In fact, insulin concentrations were lowered to a greater extent when high viscosity guar gum treatment was orally administered versus

duodenally infused in comparison to low viscosity guar gum product in healthy subjects (Leclère, et al., 1994).

Based on these findings, various viscous polysaccharides with strong viscosity-enhancing and/or gelation properties have been explored as additives to food products as a means to control satiation, satiety and energy intake and because of their therapeutic potentials in hyperglycemia, hypercholesterolemia and obesity. However, poor palatability has presented a technical challenge for some such as guar gum (Ellis, et al., 1991). Guar gum has been the most investigated due to its large market in food industry (Butt, et al., 2007). It produces higher viscosity than locust bean gum, pectin or carboxymethyl cellulose (Brenelli, et al., 1997; Chudzikowski, 1971), and is highly effective in controlling glycemia and lipid profile and in improving insulin sensitivity in various populations (Ebeling, et al., 1988; Jenkins, et al., 1977; Peterson, et al., 1987). Guar gum is also effective in inducing prolonged satiety and eventually promoting weight loss in obesity (Krotkiewski, 1984; Tuomilehto, et al., 1980). However, addition of guar gum to foods has not been successful due to its low palatability at levels needed to be physiologically functional. Guar gum is typically added to food products at levels < 1% as a thickener and stabilizing agent (Apling and Ellis, 1982). Sensory characteristics of guar gum are deteriorated at higher levels such as those used in clinical studies (3-5%) (Ellis, et al., 2001). Due to their viscous nature, their heat-stable gel-forming potentials under proper acidic conditions, their natural abundance and their superior palatability relatively to other viscous fibers, alginates are currently being applied to foods on the assumption that they will provide a wide range of functional properties and contribute to health benefits.

## D. Alginates: definition, characteristics and food applications

### 1. Definition of alginates

Alginates represent a family of non-repeating unbranched exopolysaccharides gelling fibers, composed of various amounts of (1-4)-linked β-D-mannuronic acid and its C5-epimer α–L-guluronic acid (Rehm, 2005). The term alginate is usually used for the salts of alginic acid, but it can also refer to all derivatives of alginic acid and to alginic acid itself. The first information about the sequential structure of alginates came from the work of Haug and colleagues (Haug, et al., 1966; Haug and Smidsrød, 1965). By partial acidic hydrolysis and fractionation, they separated alginates into three fractions of widely differing composition distributed either as blocks of continuous β-D-mannuronic acid residues (M-blocks) or as α–L-guluronic acid residues (G-blocks) or as alternating residues (MG-blocks or alternating blocks).

Alginates are abundant in nature, as they are synthesized by brown seaweeds from the family of Phaeophyceae and by soil bacteria belonging to the genera *Pseudomonas* and *Azotobacter*as capsular polysaccharides (Draget, et al., 1997). Knowing that bacteria can only produce alginates with more extreme and variable compositions such as up to 100% mannuronate and that the biological functions of alginates in bacteria are not fully understood (Sutherland, 1977), the most commonly available alginates are those extracted from brown seaweeds. The processes required for alginate extraction from brown seaweeds are relatively simple and straightforward (McHugh, 2003). The major outcome of the extraction process is dry and powdered sodium alginate. The main rationale of the extraction process of alginates from seaweeds is to convert all alginate salts to sodium salts, dissolve them in water and remove all seaweed residues by filtration. As a first step, either an acid or a calcium salt is added to generate



 

the water-insoluble alginic acid or calcium alginate respectively. An acid is added to calcium alginate in order to convert it to alginic acid. Alginic acid is then easily isolated, and is treated with alcohol and sodium carbonate to be subsequently converted to sodium alginate. Since sodium alginate does not dissolve in the alcohol-water mixture, it can be separated from the mixture, dried and milled to an appropriate particle size for industrial use. Sodium alginate, as the major product of this extraction process, is the main form of alginate studied and in use. However, it should be noted that smaller quantities of alginic acid and ammonium, calcium, potassium and triethanolamine salts are also produced (McHugh, 1987).

Composition of alginate polymers was found to differ by alginate sources. For instance, the presence of G-blocks is similar in algal alginates and in alginates derived from *Azotobacter vinelandii* (Skjåk-Braek, et al., 1986). While alginates from *A. nodosum*, *L. japonica* and *Macrocystis pyrifera* have a low content of G blocks, alginates from Pseudomonads completely lack them. Moreover, polymer sequence differs among various tissues of the same algae. For example, in *Laminaria hyperborea*, algae which grow in very exposed coastal areas, the stipe and holdfast have a very high guluronic acid content. On the other hand, the leaves of the same algae have alginates with a lower G content. The distribution of blocks along alginate molecules also depends on the age of algae (Indergaard and Skjak-Braek, 1987) and varies according to their seasonal and growth conditions (Haug, 1964; Indergaard and Skjak-Braek, 1987). Thus, depending on the physico-chemical characteristics of alginates required by the industry, their natural source is selected.

## 2. Characteristics of alginates

Alginates are viscous water-soluble fibers, with a wide range of molecular weights and degrees of polymerization and with strong gelling properties under proper pH conditions. Viscosity and gel formation are the most industrially relevant properties of alginates. Sodium alginate is available in low-, medium- and high-viscosity grades (McHugh, 2003). In addition to being dependent on the severity of extraction conditions, viscosity may also vary with the algal species in use. For instance, *Macrocystis* can give medium to high-viscosity alginates, whereas *Sargassum* usually provides low viscosity alginate products. While *Laminaria digitata* generates a soft to medium strength gel, *Laminaria hyperborea* gives strong gels.

Viscosity is also strongly shaped by the degree of polymerization of alginate molecules (McHugh, 1987). The degree of polymerization of an alginate is a measure of the average molecular weight of the molecules and reflects the number of uronic acid units per average chain. Natural, bacterial and enzymatically tailored alginates have been described with polydisperse molecular weights, as they are synthesized by polymerase enzymes rather than coded for in the DNA of the organism and undergo substantial depolymerisation during extraction (Draget, 2009). Considering all these determinants, manufacturers have the chance to produce alginates of very specific viscosity properties for particular applications.

Alginate gels either by being cross-linked in the presence of multivalent cations such as calcium ions (ionic gelation) or by formation of intra-molecular hydrogen bonds when the pH is lowered below 3.5 (acid gelation) (Draget, et al., 1994). Acid gels have not been as comprehensively studied as calcium gels, because they have been characterized with half the strength of calcium gels for equivalent alginate concentrations (King, 1983) and they are more limited in their application (McHugh, 1987). The affinity for multivalent cations depends on



 

alginate composition, being an exclusive property of polyguluronate rather than polymannuronate (Haug, 1964). The carboxylate functional groups of G units in the alginate molecule have appropriate spacing and geometry for cation binding. In fact, G blocks can adopt a spatial conformation that favors ionic cross-linking and that facilitates the formation of stronger gels in the presence of multivalent cations(Smidsrod and Draget, 1996). The chelation of ions by G blocks has been described by the "egg box" model, in which each divalent ion interacts with two adjacent G residues as well as with two G residues in an opposing chain generating a 4:1 ratio between G residues and the cations (Smidsrod, 1973). Calcium has found greatest popularity as the divalent ion for gel formation, since calcium salts are cheap, readily available and non-toxic (McHugh, 1987). Upon ingestion, solubilisation of the calcium salt in acidic gastric fluid liberates additional free calcium ions, which also become available to cross-link with alginate. Gel formation depends on the rate of release of free calcium ions and their interaction with alginate upon acidification in the stomach. Under physiological conditions, gel formation is optimal within a small pH range achievable in the stomach (Wolf, et al., 2002). Once the chyme pH is above 5 in the intestine, the gel is broken. When pH becomes so low, acid-catalyzed gel intramolecular depolymerisation can also take place (Draget, et al., 1994).

In contrast to most gelling polysaccharides, alginates can form strong gels without the need for heat and the formed gels do not melt when heated (Smidsrod, 1973). This is in contrast to agar gels, where water must be heated to around 80$^{o}$C to dissolve the agar and then gel forms when temperature cools below 40$^{o}$C (McHugh, 2003). However, a prolonged heat treatment at low or high pH may induce a series of chemical degradation processes and thus destabilize the alginate gel. Moreover, stability of alginate molecules is also dependent on their degree of

polymerization and thus viscosity (Draget, 2009). Alginates with higher degree of polymerization and hence viscosity are less stable than those with lower ones. Indeed, low viscosity sodium alginates showed no observable changes over 3 years when stored at 10-20$^{o}$C, while medium viscosity ones showed 10% loss at 25$^{o}$C and 45% loss at 33$^{o}$C after one year and high viscosity alginates displayed the least stability.

Grouping all these distinct characteristics of alginate polymers together, a notable increase in the number of alginate applications has occurred in recent years (Draget, 2009). Commercial alginates are mainly produced from algal sources, including *Laminaria hyperborea*, *Macrocystis pyrifera*, *Laminaria digitata*, *Ascophyllum nodosum*, *Laminaria japonica*, *Eclonia maxima*, *Lessonia nigrescens*, *Durvillea Antarctica* and *Sargassum* species. Pharmaceutical, food and technical applications (such as in print paste for the textile industry) are the main market areas for alginates. The wide utilization of alginates in food applications is discussed in the following.



### 3. Food applications of alginates

Alginates are widely used in the food industry for their ability to retain water and for their gelling, viscosifying and stabilizing characteristics especially in the presence of calcium salts. Food applications of alginates have also widely occurred due to their safety (Strugala, et al., 2004). Various salts of alginates, including alginic acid and ammonium, calcium, potassium and sodium salts, have been granted the status of Generally Recognized As Safe. In addition, The Joint Expert Committee of Food Additives of the Food and Agriculture Organization of the United Nations/World Health Organization has also issued specifications for alginates, allowing an Acceptable Daily Intake of 50 mg per kg body weight per day for alginic acid (Food and Agriculture Organization of the United Nations and World Health Organization, 1965).

Acceptable limits for sodium alginate daily intake are not yet defined. However, long-term observations in rodents and men showed no adverse events with the consumption of sodium alginate even at large doses. A study by Millis and Reed (Millis and Reed, 1947) reported that healthy adults were given 8g of sodium alginate daily for seven days without untoward effects. No allergic reactions and only minimal gastrointestinal adverse events have been described with the consumption of alginates (Anderson, et al., 1991), and ratings of gastrointestinal symptoms are similar between alginate fiber and control products (Georg Jensen, et al., 2011; Georg Jensen, et al., 2011; Mattes, 2007; Pelkman, et al., 2007; Williams, et al., 2004; Wolf, et al., 2002). Alginate fiber is perhaps a more tolerated fiber source than other viscous fibers such as guar gum and pectin because it is more slowly fermented (Brownlee, et al., 2005; Wolf, et al., 2002).

Alginates add a variety of functional properties to foods and beverages, from providing gelling characteristics for desserts and dairy products to thickening sauces, serving as gelatin replacements and constituting the basis of restructured products (Sime, 1990). Thickening is useful in sauces, syrups, ice cream toppings, pie fillings and cake mixes, whereas gel formation is useful for the preparation of instant milk desserts and jellies, bakery filling cream, fruit pies, animal foods and reformed fruit (King, 1983). Alginates have been also used as stabilizing agents due to their general colloidal properties. Dessert gels, such as bakery creams, jams and jellies, and ice cream are prepared using alginates as stabilizers (Protan, 1986). As approved by the US Department of Agriculture, alginates are also utilized as binders in restructured meal products such as chicken nuggets (McHugh, 1987). The binder mixture consists of sodium alginate, calcium carbonate, lactic acid and calcium lactate, which can replace the traditional mixture usually used and composed of sodium chloride and phosphate salts. Thus, the use of the

alternative alginate-based mixture provides a means of reducing sodium levels in these restructured products. One of the most recent developments is the use of alginate in spherification, a novel technique in gastronomy consisting of shaping liquids into spheres through the interaction of sodium alginate with calcium chloride to form various fabricated food products.

Minimal food uses have been reported for alginic acid itself as well as for potassium, ammonium and calcium alginates. Sodium alginate is the form with greatest industrial application (McHugh, 1987). Several attempts to chemically modify alginate and vary its physico-chemical properties have been reported in order to widen its food applicability. Among these is propylene glycol alginate (PGA), which is the only derivative of alginic acid with wide industrial use and acceptance as a food additive. It is an ester derivative obtained by reaction of propylene oxide with some uronic moieties of alginate (Yilmazer, et al., 1991). Esterification occurs at the carboxylic acid groups of the alginate chain, mainly with the primary hydroxyl group of propylene glycol (Noto and Pettitt, 1980). Varied degrees of esterficiation can be achieved, depending on reaction temperatures and ratios of propylene oxide to alginic acid. Although a product with 60-70% esterification is satisfactory for industries, products with 80-90% esterification are more useful in acidic conditions for short term applications. Propylene glycol alginate is largely used as a thickener and stabilizer in several food applications mainly because of its solubility in acidic conditions and low sensitivity to the presence of divalent ions. In addition, the hydrophobic character introduced by the propylene glycol moiety allows this modified polysaccharide to function as emulsifier and surfactant (Yilmazer and Kokini, 1991). It

is thus used more often than sodium alginate in acidic products such as beer, salad dressings and fruit beverages.

Although alginates are widely used in foods to improve functionality of food formulations, their physiological functionality has received more attention lately. The combination of the physico-chemical characteristics of alginates, including their viscosity- and gel-forming properties in the stomach and small intestine, makes them possible functional food ingredients for modulation of gastrointestinal signals that control satiation, satiety, food intake and glycemia (Hoad, et al., 2004; Solah, et al., 2010).



## E. Role of Alginates in Food Intake and Glycemic Regulation

As viscous and gel-forming fibers, alginates were hypothesized to play a role in the regulation of satiety, food intake and glycemia and in the management of body weight. Despite the theoretical potential of alginate to aid in weight management, a number of conflicting findings exist with respect to its physiological role in modulating markers of satiety and energy intake and determinants of glucose homeostasis.

### 1. Alginates, satiety and energy intake

By interacting with mechanical and chemical stimuli in the stomach and small intestine, alginates were hypothesized to impact hunger, satiation and satiety signals. The existing literature suggests that when properties of alginate products are optimal, they are likely to be successful in reducing food intake. Clearly, the physico-chemical properties of alginate fibers, their dose, their volume and their food vehicle must be optimized in order to produce sufficient gel strength and satisfactory effects on satiety and subsequent food intake.

Randomized controlled trials on the effects of alginates on satiety and energy intake have not provided consistent outcomes. Several randomized controlled studies have examined the effects of alginates on satiety feelings and energy intake (Georg Jensen, et al., 2011; Hoad, et al., 2004; Mattes, 2007; Odunsi, et al., 2010; Paxman, et al., 2008; Pelkman, et al., 2007; Peters, et al., 2011; Solah, et al., 2010), but findings varied dependent on whether alginate-based matrices were consumed acutely or repeatedly over several days. While two studies found no effect on satiety feelings and caloric intake (Mattes, 2007; Odunsi, et al., 2010), another one did (Georg Jensen, et al., 2011). Moreover, two studies reported reduced energy intake (Paxman, et al., 2008; Pelkman, et al., 2007), and others showed only a decrease in hunger sensations without reporting on food intake (Hoad, et al., 2004; Peters, et al., 2011; Solah, et al., 2010). Although most used a strong-gelling sodium alginate with a high guluronic:mannuronic acid ratio for the preparation of their treatments, not all of the studies reported either on the type of alginate used, its viscosity, its gelling properties and its characteristics or on the resultant gel strength. As previously indicated, the strength of the gel formed in the stomach in response to ingestion of viscous fibers has a strong impact on satiation and satiety outcomes through regulation of the extent of gastric distension and delay in gastric emptying and may be one of the factors accounting for the varying outcomes.

Acute studies consistently reported enhanced satiety with alginate supplements. An early study by Hoad (Hoad, et al., 2004) on healthy volunteers reported that the ingestion of viscous milk-based meal replacer beverages composed of 1% by weight of alginate or guar gum, which is known to generate an acid-resistant gel, induced a greater sense of fullness in comparison to the control. More importantly, the guluronate-rich alginate, with the stronger gelling capacity,

had a more significant impact on fullness than the weak-gelling alginate primarily based on mannuronic acid (Hoad, et al., 2004). Since only the strong-gelling alginate and not guar gum suppressed postprandial hunger sensations, the superiority of agents that gel on contact with acid in regulating satiety was highlighted. Furthermore, the physical characteristics of a drink (viscosity and/or gel strength) had a greater impact on hunger in healthy adults than its protein content (Solah, et al., 2010). At low protein levels (<3 g per 250 mL), subjects reported reduced hunger from the high-viscosity compared to the low-viscosity sodium alginate-based calcium-rich drink (0.25 g per 250 mL) (Solah, et al., 2010). In addition, the high-viscosity low-protein alginate-based drink reduced hunger to a greater extent than the low-viscosity high-protein preload (30 g per 250 mL).

The effects of alginates on hunger and satiety sensations were reported to increase dose-dependently (Peters, et al., 2011). The consumption of ready-to-drink meal replacement shake for breakfast, supplemented with high-guluronate alginate both at 0.6% and 0.8%, significantly reduced hunger and increased fullness responses in healthy volunteers in comparison to the control shake (Peters, et al., 2011). However, effects were less pronounced following the 0.6% than the 0.8% alginate shake.

The acute impacts of alginate consumption not only on satiety sensations but also on acute energy consumption were demonstrated by Jensen (Georg Jensen, et al., 2011), using higher alginate concentrations dissolved in a higher volume of water for optimal hydration of the fiber. In this placebo-controlled double-blind crossover trial, healthy young Danish subjects were randomly assigned to receive a 3% preload concentration of either low volume (9.9 g sodium alginate in 330 mL) or high volume (15.0 g sodium alginate in 500 mL) of a sodium alginate-

based beverage or of an isovolumetric placebo beverage 30 min before a fixed breakfast and an *ad libitum* lunch (Georg Jensen, et al., 2011). While the low volume alginate beverage had no effect on subjective appetite and only suppressed energy intake by 8.0%, the high volume alginate beverage increased satiety, decreased hunger and the feeling of prospective food consumption in addition to reducing energy intake by 5.0%. The lower effect of the 500 mL alginate beverage on food consumption was attributed to the fact that the beverages were not supplemented by calcium ions that are normally added to induce cross-linking and gelation (Draget, 2009), relying entirely on stomach acid for this function. Furthermore, the 500 mL beverage may have likely diluted the stomach acid (Georg Jensen, et al., 2011) and the sodium alginate may not have achieved a sufficient gel strength, which may be necessary for the physiological effects of alginate on satiety (Hoad, et al., 2004; Peters, et al., 2011).

Although not strongly established, a correlation between measures of hunger or fullness and improved outcomes for weight loss has been described in some studies (Drapeau, et al., 2007; Womble, et al., 2001). Whether the suppressive effects on hunger and food intake observed in the acute phase following consumption of alginate-enriched products could be extrapolated to a consistent decrease in energy intake and hence a negative energy balance in the long term has not been well explored. Some studies described significant reductions in energy intake following repetitive consumption of alginate-enriched foods. For example, ingesting calcium-gelled alginate-pectin blend (1.0 or 2.8 g of alginate per 237 mL) twice per day, one dose before breakfast and a second around 2.5 hours after lunch, over 7 days significantly reduced spontaneous food intake by 10% (272 kCal) without any meaningful change in subjective measures of satiety in overweight and obese women (Pelkman, et al., 2007). Similarly, in the

study of Paxman (Paxman, et al., 2008) on free-living healthy subjects, the consumption of an alginate beverage (100 mL), containing 1.5 g of sodium alginate (65-75% guluronic acid) with 0.7 g of calcium carbonate and specifically designed to undergo enhanced intragastric gelation without relying on gastric acid secretion (gel strength of 30 N, referring to the penetration force of the gel up to a depth of 20 mm using texture analyzer), before breakfast and evening meals over 7 days resulted in a significant 7% (135 kCal) daily energy intake reduction in comparison to the control. Mean intakes of carbohydrate and protein as well as of sugar, fat and saturated fat significantly decreased following alginate preload consumption irrespective of gender and body mass index, while satiety data were not measured (Paxman, et al., 2008). Superior energy intake suppressive effects were reported with other viscous gel-forming fibers such as guar gum. Whether under free living conditions or with fixed levels of energy intake, a daily consumption of a guar gum-based beverage providing 40 g and 20 g of guar gum respectively over 7 days reduced mean daily energy intake by 310 kCal with no changes in hunger and satiety scores and suppressed hunger scores at the low (4 MJ) not high (6 MJ) energy intake level of obese women respectively when compared with no guar gum supplementation (Pasman, et al., 1997). Although apparently superior to the effects of alginates, this difference could be attributed to two factors. First, in the latter study, energy intake was based on data recorded over the last 3 days of the 7-day intervention period and not on 7-day estimated measures food diaries (Paxman, et al., 2008) or on *ad libitum* food consumption (Pelkman, et al., 2007). Second, the dose of guar gum of Pasman (Pasman, et al., 1997) was significantly greater than that used for alginates in the other two studies (Paxman, et al., 2008; Pelkman, et al., 2007).

On the other hand, other studies reported that repeated ingestion of alginate does not have an effect on energy intake. However, these findings are likely artefacts of suboptimal experimental design including the use of inadequate type, quantity and/or food format of alginates in addition to other experimental conditions which do not favor alginate gel formation. For example, ingestion of a fiber-based breakfast bar, composed of 1.1 g sodium alginate (2% wt/wt) and 3.9 g guar gum fiber (7% wt/wt) per 55 g serving (196 kCal), given repeatedly over 5 days had no significant impacts on self-reported mean, peak or nadir hunger, desire to eat, prospective consumption or fullness ratings over each 5-h post-loading period nor on daily and cumulative dietary energy and macronutrient intake in overweight females (Mattes, 2007). However, the amount of alginate used (1.1 g) may not have been sufficient to induce adequate gelation: the majority of the studies that reported significant physiological impacts of alginates used larger quantities such as 1.5 g (Paxman, et al., 2008; Wolf, et al., 2002), 2.8 g (Pelkman, et al., 2007), 3.25 g (Hoad, et al., 2004), 5 g (Torsdottir, et al., 1991), and 9.9 g and 15 g (Georg Jensen, et al., 2011). In addition to the relatively low amount of alginate in use, the bar format would have been another contributing factor having a low availability of fibers for gelation due to their slow hydration rates and solubility. Similarly, solid food vehicle hindered the effects of alginate on satiety and food intake in Odunsi (Odunsi, et al., 2010) irrespective of the dose. CM3 alginate, a weight-loss commercial product containing sodium alginate among its ingredients, had no significant effects on satiety and total and macronutrient caloric intakes at a free choice meal when consumed daily at 1.2 g for the first 7 days and 2.4 g for the last 3 days over 10 days in overweight and obese adults (Odunsi, et al., 2010). The type of alginate was not specified, and thus its gelling potential could not be verified and evaluated. In addition to dose and food

vehicle, the presence or absence of certain food components that favor alginate gelation may also influence the effects of alginates on food intake. Although of liquid nature and with a significant amount of alginates, the absence of calcium ions in the beverage masked the effect of chronic alginate consumption on body weight in Jensen (Georg Jensen, et al., 2011). Consuming low viscous alginate fiber-based preloads of 3% concentration (500 mL) three times a day over 2 weeks as an adjuvant to a calorie-restricted diet did not produce additional body weight or waist circumference loss beyond that resulting from caloric restriction alone in obese individuals (Georg Jensen, et al., 2011). Preload beverages were based on water and thus relied solely on gastric acid secretion for gel formation due to the absence of calcium ions, which might have weakened the formed gel.

Overall, variations in the physical properties of alginate in use, including species, M/G ratio and molecular chain lengths, differently influence the viscosity of the food product, the gelling ability and strength of gel mass in the stomach and hence satiety sensations and food intake. As previously stated, alginates containing high amounts of guluronic acids form stronger gels with strong heat stability and an increase in gel strength is observed in the order of MG-blocks ≤ M-blocks < G-blocks (Draget, et al., 1997). Gel strength is also strongly determined by the presence of calcium ions and the concentration of alginate in use (Hoad, et al., 2004; Strom, et al., 2010). Weak gelling high-mannuronic acid alginates did not produce satiety, whereas strong gelling high-guluronic acid ones did (Appleton, et al., 2004; Hoad, et al., 2004; Peters, et al., 2006). In rats, total food intake and the weight of the dorsa and abdominal adipose tissue were the lowest among those given the G-rich alginate diet compared to those on diets with lower G/M ratios (Ohta, et al., 1997). Minimum gel strength seems to be required for inducing satiety according to

in vitro (Flint, et al., 2000) and in vivo experiments (Hoad, et al., 2004; Peters, et al., 2006). A minimal gel strength of 1.8 N of alginate beads under gastric conditions, referred to as the force required to compress gel beads 1 mm at a constant rate of 0.2 mm/s, was suggested as a prerequisite for a meaningful satiety effect (Peters, et al., 2011), whereas a minimal agar bead strength of 0.6 N was needed to resist antral grinding forces and induce satiety (Marciani, et al., 2000). If translated into product viscosity values, 80 to 100-fold higher viscosity is needed for a significant effect on satiety or fullness to be observed (Marciani, et al., 2000; Marciani, et al., 2001). However, whether in-product gelation, usually associated with reduced product quality and poor consumer acceptance, was prevented or not in the study determines as well the extent of effect of alginate on satiety and food intake. In the study of Peters (Peters, et al., 2011), a shelf-stable product containing the alginate together with significant amounts of calcium was used. In contrast, either alginate has been added to a calcium-containing drink immediately prior consumption (Appleton, et al., 2004; Hoad, et al., 2004; Paxman, et al., 2008; Peters, et al., 2006) or both alginate and calcium sources were separately consumed (Pelkman, et al., 2007) in other studies.

The format of the alginate-containing product, whether solid or liquid, may further affect the in vivo physico-chemical properties of alginates. Liquids are more useful delivery vehicles for alginates than solids, as they ensure that fibers are consumed in a fully hydrated form (Strom, et al., 2010). In fact, the kinetics and outcome of hydration and solubility of alginates in tablets or bars differ from those of a solution, where hydration and solubility are optimal (Draget, et al., 1994; Draget, et al., 1997; Potty, 1996). Adding alginate to liquids was reported to have a greater

effect on satiety than adding it to solids (Mattes, 2007; Odunsi, et al., 2010; Paxman, et al., 2008; Pelkman, et al., 2007).

The minimum level of alginate needed to influence satiety and subsequent energy intake when added to liquids is not well established, but levels below 0.6% of a strongly gelling alginate may not give robust benefits. Levels as low as 1% (Hoad, et al., 2004) and 0.8% (Appleton, et al., 2004; Peters, et al., 2006) of strongly gelling alginate significantly increased satiety, whereas 0.4% did not (Appleton, et al., 2004). Levels as low as 0.6% of high-guluronate alginate increased satiety although effects were clearly less effective than 0.8% (Peters, et al., 2011). Thus, alginates may strongly contribute to satiety and food intake regulation at levels that do not compromise the oro-sensory attributes of the food product. Minimal deterioration in the palatability of alginate products has been described in some studies at concentrations exceeding 1% (Georg Jensen, et al., 2011; Hoad, et al., 2004; Mattes, 2007; Williams, et al., 2004) but not in others in which concentrations lower than 1% were used (Peters, et al., 2011).



## 2. Mechanisms of action of alginate

The physiological effects of alginates have been mainly attributed to viscosity or gel formation or both; however, the relative contribution of each is unclear. Modulation of gastric measures and regulation of glycemia were suggested as the major modes of action of alginates on satiety and energy intake, and are elaborated in the following.

### a. Alginate and gastric measures

Based on the existing literature, gastric distension and not delayed gastric emptying was established as the gastric measure of great significance in explaining the satiating characteristics

of alginates. Gastric distension is strongly associated not only with the viscous nature of alginates but also with their gel-forming capacity (Hoad, et al., 2009; Schroeder, et al., 2009). In fact, high viscosity gel-forming fibers form lumps in the stomach, increase gastric volume and enhance fullness sensation to a greater extent than low- or high-viscosity fibers that do not gel and that are more homogenously diluted in the stomach. Using magnetic resonance imaging studies, 1% of strong-gelling alginate formulations increased volume of gelled lumps in the gastric antrum in comparison to weak-gelling ones (Hoad, et al., 2004). As previously discussed, increased gastric distension activates satiation signals either via the vagal and splanchnic nerve or via stimulation of chemo- and mechanoreceptors in the gastric body and fundus (Marciani, et al., 2001; Park and Camilleri, 2005; Powley and Phillips, 2004).

When formed within the stomach, gel lumps can influence the delivery of nutrients to the small intestine through two different mechanisms. First, gel lumps trap nutrients inside the stomach releasing them slowly as the lumps are solubilized (Ohta, et al., 1997; Tomlin, 1995). Second, gel lumps persist into the small intestine and break up lower down in the bowel, delaying nutrient absorption in comparison to non-gelled meals. When alginate gel lumps leave the stomach and increase the viscosity of the intestinal lumen, the unstirred water layer at the luminal surface is thickened and the contact between food and digestive enzymes is decreased, delaying the digestion of food, slowing the rate of nutrient absorption and removal from the intestinal lumen and shifting them further down the small intestine (Dikeman and Fahey, 2006; Hlebowicz, 2009; Lin, et al., 1997). In addition to limiting the contact of food with digestive enzymes, alginates reduce the activity of certain digestive enzymes including pepsin and trypsin (Maljaars, et al., 2007). All these processes were found to enhance the release of several

appetite-regulating hormones from distal intestine including PYY and GLP-1 (Maljaars, et al., 2007; Maljaars, et al., 2008). However, in the study of Odunsi (Odunsi, et al., 2010) on overweight and obese individuals, chronic ingestion of alginate in the form of a pill over 10 days was not found to affect the profile of various appetite hormones including acylated ghrelin, CCK, GLP-1 and PYY. As it is the only study to evaluate the effects of alginate on gut hormones, any influence of alginates on these hormones cannot be ruled out because the kinetics of hydration and solubility of alginates in a pill format may not reflect their effects in foods or beverages.

Delayed gastric emptying cannot be yet established as an underlying mechanism of action of alginate fiber due to inconsistencies in findings. While a delayed gastric emptying rate measured by aspirated radioactive gastric content was described after alginate administration at 2% concentration (Torsdottir, et al., 1991), gastric emptying did not change after ingestion of 1% alginate-enriched preloads in another intervention using the well-validated scintigraphy method (Hoad, et al., 2004). Discrepancies in findings could be attributed either to the different methodologies used to evaluate gastric emptying or to the inadequate alginate concentrations.

In addition to the effects of alginate fibers on gastric measures affecting food intake regulation, their effects on glycemic control has been also explored because of the glucostatic theory of hunger control and because of the need to control blood glucose excursions and reduce insulin demand in type 2 diabetes. Regulation of glucose oscillations in the postprandial period as a result of slowed carbohydrate digestion and absorption were listed among the probable mechanisms by which alginates may modulate satiety sensations, food intake and glucose homeostasis.



 

**b. Alginate and glycemic control**

Data as a whole suggest that alginates may have significant potential in dampening glycemic responses to carbohydrates. Relative to other viscous fibers, lower doses of alginates seem to be needed for beneficial effects on glycemia to be observed. Although reduced glycemic responses were noted following the consumption of other viscous fibers such as guar gum, psyllium and β-glucan, high doses were required (Braaten, et al., 1991; Holt, et al., 1979; Jenkins, et al., 1978; Pastors, et al., 1991).

Several studies have described blunted glycemic responses to alginate ingestion. In various animal models, sodium alginate reduced intestinal absorption of glucose (Jiménez-Escrig and Sanchez-Muniz, 2000; Kimura, et al., 1996; Vaugelade, et al., 2000). Alginate formulations fed to male Wistar rats improved glucose and insulin levels in response to glucose tolerance tests (Kimura, et al., 1996). Similar findings were reported in humans, whether healthy, obese or type 2 diabetic. Ingestion of 5 g of sodium alginate in a 340 kCal beverage reduced the postprandial rise in blood glucose and serum insulin by 31% and 42% respectively in well-controlled type 2 diabetic males (Torsdottir, et al., 1991). A comparable suppressive effect was reported in healthy individuals, where the 500 mL 3% sodium alginate beverage reduced glucose incremental area under the curve (iAUC) by 40% without decreasing insulin responses in comparison to the 500 mL control beverage (Georg Jensen, et al., 2011). In obesity, alginates restored glucose uptake in overweight and obese individuals to levels observed in healthy participants (Paxman, et al., 2008). Reduced rates of intestinal glucose uptake and an abolishment of the correlation between body fat percentage and area under the glucose response curve post meal consumption in

subjects with elevated body fat levels were found following consumption of 1.5 g of sodium alginate in the presence of calcium carbonate in a 100 mL beverage.

Ingesting alginates in solid food vehicles also brought about a drastic reduction in postprandial plasma glucose levels. In the study of Williams (Williams, et al., 2004) on healthy non-diabetic volunteers, pre-prandial consumption of a nutritional crispy bar (50 g carbohydrates) containing a novel induced viscosity fiber (5.5 g of guar gum and 1.6 g of sodium alginate) reduced incremental peak blood glucose concentrations by 30% and glucose iAUC by 33% without any gastrointestinal intolerance. It should be noted, however, that these effects may not be attributed with certainty to sodium alginate. Experimental products exceeded the controls not only in sodium alginate but also in guar gum content, and an increase in either of these parameters is known to dampen blood glucose level excursions independently (Wolf, et al., 2002; Wolf, et al., 2003). Nonetheless, Wolf and colleagues (Wolf, et al., 2003) demonstrated that sodium alginate downregulates postprandial glycemic responses independently of total fiber content. The alginate beverage (1.5%) produced lower postprandial glucose concentrations than a control treatment of equal fiber content. Furthermore, an alginate-containing diet reduced postprandial glycemic response in dogs to a greater extent than diets containing an equivalent amount of oat and soy fiber by weight as well as diets containing more than twice the weight content of soy fiber (Murray, et al., 1999). Taken together, these studies suggest that the effect of alginate on reducing postprandial glycemic responses is at least as good as, and in some cases exceeds, that of other viscous fibers.

Mechanisms suggested to explain the hypoglycemic properties of alginates include regulation of glucose absorption via their alginic acid byproduct, gel formation in the stomach and to a

lesser extent delayed gastric emptying. Free alginic acid, a byproduct of alginate hydrolysis by gastric acid, has the ability to inhibit glucose absorption by acting on $Na^+$-dependent glucose transporters in the small intestine (Kimura, et al., 1996). Alginic acid enhanced $Na^+$ excretion into the feces of rats fed high salt diets, and inhibited $Na^+$ absorption in the small intestine (Kato, et al., 1991). Moreover, attenuated glycemic responses may also be explained by the formation of viscous gel in the stomach. Glycemic and insulinemic concentrations were dampened in response to an experimental acid-induced viscosity complex (alginate:citrate:calcium) incorporated into a glucose beverage (Wolf, et al., 2002). Even 5 g of an enzymatically-induced viscosity guar gum product, added to a 50 g starch meal, stabilized blood glucose levels and reduced their early phase excursion when compared to fructose or white bread (control) in healthy non-diabetic adults (Wolf, et al., 2003). However, inherent viscosity of the ingested product is not the only determinant. Gel formation in the presence of dietary calcium in the stomach is another factor to consider. In diabetic rats, diets containing both sodium alginate and calcium induced the lowest postprandial glycemic responses in comparison to the diet free of alginate and calcium, the diet with alginate and without calcium and the diet with calcium and without alginate (Ohta, et al., 1997).

The effect of alginates on glycemia may also be related to their ability to slow gastric emptying, although the literature is not conclusive on this point. Slower gastric emptying, assessed by aspirated radioactive gastric content, was documented with 5 g alginate supplementation in controlled type 2 diabetics, concomitant with a strong correlation between the prolongation effects of sodium alginate on gastric emptying and the attenuation of glucose responses (Torsdottir, et al., 1991). Paradoxically, two studies concluded that the mechanism of

action of alginate is not dependent on gastric emptying. Hoad and colleagues (Hoad, et al., 2004) measured gastric emptying by magnetic resonance imaging, and found no difference between the rates induced by alginate-containing beverages with strong or weak gel strength (3.25 g), guar-containing beverages and milk. Similarly, Paxman (Paxman, et al., 2008) concluded that sodium alginate (1.5 g) was unlikely to act through slowing gastric emptying since it did not alter the time taken to reach peak glucose levels in the plasma. As previously indicated, inconsistencies in these findings may be explained by the different alginate doses in use and the various techniques applied to measure gastric emptying.



## F. Conclusions and Future Directions

In conclusion, a significant potential of alginates, more precisely sodium alginates, in the regulation of satiety, food intake and glycemia when supplemented to foods has been illustrated. However, uncertainties remain regarding the utility of alginates for body weight and glycemic management in the long term. Physiological adaptations to chronic gastric distension, induced by long-term consumption of gel-forming viscous fibers such as alginates, may hinder any effects of chronic alginate consumption on food intake, body weight and glucose homeostasis and thus should be taken into consideration.

The incorporation of alginates into food products seems to be promising, offering physical, chemical, sensorial and physiological advantages over other viscous and gel-forming fibers. However, gel strength, dependent on the species, the M/G ratio and the molecular chain lengths, food vehicle and dose of alginate shape its effects and should be further addressed in future

studies. Thus, in addition to their physico-chemical functionality as a food ingredient, the physiological significance of alginates in foods needs further exploration.



 

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