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The effects of weight loss strategies on gastric emptying and appetite control

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Abstract

The gastrointestinal tract plays an important role in the improved appetite control and weight loss in response to bariatric surgery. Other strategies which similarly alter gastrointestinal responses to food intake could contribute to successful weight management. The aim of this review is to discuss the effects of surgical, pharmacological and behavioural weight loss interventions on gastrointestinal targets of appetite control, including gastric emptying. Gastrointestinal peptides are also discussed because of their integrative relationship in appetite control. This review shows that different strategies exert diverse effects and there is no consensus on the optimal strategy for manipulating gastric emptying to improve appetite control. Emerging evidence from surgical procedures (e.g., sleeve gastrectomy and Roux en-Y gastric bypass) suggests a faster emptying rate and earlier delivery of nutrients to the distal small intestine may improve appetite control. Energy restriction slows gastric emptying, while the effect of exercise-induced weight loss on gastric emptying remains to be established. The limited evidence suggests that chronic exercise is associated with faster gastric emptying which we hypothesise will impact on appetite control and energy balance. Understanding how behavioural weight loss interventions (e.g., diet and exercise) alter gastrointestinal targets of appetite control may be important to improve their success in weight management.

Introduction

The World Health Organization estimates that by 2015 approximately 2.3 billion adults will be overweight and more than 700 million will be obese (1). Strategies which lead to a decreased energy intake and/or increased physical activity are commonly advised in an attempt to combat the epidemic; yet often only modest weight loss is achieved (2-3). This may be due in part to compensatory responses in energy intake (for a review of the complete range of responses to an energy deficit see (4)). Bariatric surgery is associated with sustained weight loss and a persistent reduction of energy intake (5) but in light of the large number of patients that qualify for a surgical procedure, the associated costs and lack of surgical resources, surgery remains impractical on a population level. However, in addition to gastric restriction, some procedures appear to reduce weight by changing the profile of circulating gut peptides implicated in appetite control (6-8) suggesting there is potential for substantial and sustainable weight loss with other strategies if these effects can be replicated. Recent evidence suggests this increased gut peptide response may be due in part to alterations in the emptying rate of the gastric remnant (9-15). An increased understanding of the effects of diet, exercise, pharmacological and surgical weight loss interventions on gastrointestinal targets of appetite control may help to explain the variability in compensatory responses and could facilitate the more effective use of non-surgical strategies in weight management in future.

Energy homeostasis: tonic and episodic processes

To understand why changes in energy intake might vary with different strategies, the processes controlling food intake should first be considered. It is widely recognised that energy homeostasis is governed by a complex neuroendocrine feedback system between the periphery and the central nervous system which involves the interaction of tonic (i.e., long term) and episodic (i.e., short term) signals with a network of hypothalamic, mesolimbic, and hindbrain circuits (16). While knowledge of the neurocircuitries governing metabolic homeostasis may also be instrumental for developing more effective antiobesity strategies (for a review see (17)), the focus of this review concerns the responses of peripheral signals to weight loss. Although tonic signals can influence episodic signals (18-19), both processes appear to have different roles in the control of appetite (20), and are discussed separately in this section**.**

Tonic signals, of which leptin and insulin are well established, reflect the metabolic state of adipose tissue (20) and appear to respond similarly to weight loss, regardless of the type of weight loss intervention. In response to an energy deficit induced by bariatric surgery (21-23), diet (22, 24-26) and/or exercise (27-31), leptin and insulin levels decrease, which would be expected to stimulate appetite. This increase in appetite can be reduced by exogenous administration of leptin (32). These findings, together with evidence of tonic signals responding to changes in energy availability (33-34)

suggest that tonic signals respond primarily to changes in energy balance and body weight, and that their primary role may be to resist energy deficits.

Episodic signals including gastric distension, and orexigenic (ghrelin) and anorexigenic peptides, arise largely from the GI tract and oscillate periodically with the act of eating (20). Ghrelin, unlike other gut peptides detailed in this review stimulates appetite and rises before meals suggesting a role in meal initiation (35). Some evidence suggests that it is the state of energy balance (i.e,. in energy balance or in negative energy balance) that influences fasting ghrelin levels (21, 33-34). Fasting levels of ghrelin increase in response to diet- and exercise-induced energy deficits (30, 36-38). Following bariatric surgery, changes in ghrelin levels are equivocal (39). However, in one study increased fasting ghrelin levels were observed in individuals who were in negative energy balance and not in those in energy balance (21), suggesting the energy balance state could explain some of the ambiguity in findings. Other evidence suggests that fasting appetite sensations respond to changes in energy availability and body weight. Data collated from several weight loss intervention studies shows that fasting appetite sensations are strongly associated with body weight changes (40). However, meal-induced appetite responses are not strongly associated with energy availability or body weight (33-34, 40-41). In essence these are two different measures. The fasting state reflects the homeostatic energy state after a period of reduced body energy (exercise-induced energy expenditure or food deprivation) and the postprandial state reflects the interactions between the physiologic system and the physiologic action of food on satiety signalling (20, 41). Changes in postprandial appetite sensations may therefore occur in response to the direct effects of the weight loss intervention *per se* and could help to explain why changes in energy intake vary with different weight loss strategies. The changes in episodic signals implicated to have a role in meal induced appetite responses are discussed further.

Episodic signals are typified by mechanical factors such as gastric distension and gut peptides such as cholecystokinin (CCK) (42) both of which may be influenced by the rate of gastric emptying. Numerous reviews have considered the effects of weight loss strategies on appetite related gut peptides (see (23, 43-45)). This review will concentrate on the overlooked issue of gastric emptying; gut peptides will also be discussed because of their integrative relationship in appetite control. The role of gastric emptying in appetite control is discussed and relationships between changes in gastric emptying, gut peptides and appetite in response to different weight loss strategies highlighted. A particular emphasis is placed on lifestyle interventions and future directions for weight management.

Gastric emptying and appetite control

Persuasive evidence suggests that gastric emptying influences appetite and energy intake (46-49). As food enters the stomach and subsequently empties into the small intestine, a variety of factors

including gastric distension, nutrient stimulation of intestinal mechanoreceptors and chemoreceptors (see (50-51)) and several gut peptides released from the GI tract contribute to satiation (control of meal size) and satiety (post-meal inhibition of eating). Although it is intuitive that a faster gastric emptying leads to increased appetite, the role of gastric emptying in appetite control is complex. Gastric distension influences appetite by triggering stretch and tension mechanoreceptors which relay information to the brain (see (52-53)). There is a close relationship between the sensation of fullness and antral distension (54-55). Furthermore, food intake at a buffet meal has been shown to be inversely related to the volume of gastric contents remaining from a previous meal (56). These findings suggest that an accelerated rate of gastric emptying and hence reduced gastric distension might predispose to overeating. However, in addition to gastric distension, the presence of nutrients in the small intestine is critical to satiation and satiety (57). A number of gut peptides are released in response to intestinal nutrients and act by entering the bloodstream and indirectly via the vagus nerve to inhibit appetite (58-59). After food intake, CCK is released into the circulation from endocrine I-cells of the duodenum and the jejunum (60) whereas glucagon-like peptide-1 (GLP-1) and polypeptide YY (PYY) are released from L cells located mainly in the distal small intestine. Both GLP-1 and PYY show a biphasic response to meal ingestion (59). It is most likely duodenal nutrients initiate a neural and/or humoral signal to the distal gut contributing to their early release (61-64), which is then followed by direct nutrient stimulation of L cells in the ileum (59, 65). In the early postprandial period, a more rapid gastric emptying is directly correlated with increases in plasma levels of CCK (66-67), glucagon-like peptide-1 (GLP-1) (11, 62) and peptide YY (PYY) (67-68). Further evidence suggests a threshold rate of gastric emptying exists which must be exceeded to stimulate GLP-1 release (62). Upon release GLP-1, PYY and CCK in turn act to inhibit gastric emptying (69) but the inhibition of gastric emptying is not necessary for the control of food intake by intestinal stimulation (51, 70) and a direct effect on satiety centres is also very likely (51, 70-71). In contrast, ghrelin acts to accelerate gastric emptying (72). However, a more rapid gastric emptying rate is correlated with lower postprandial ghrelin concentrations (73-74), which in turn are associated with reduced appetite (73). Taken together these findings suggest that a slowing of the emptying rate might increase and prolong gastric distension but also result in a delayed or reduced release of CCK, PYY and GLP-1 and reduced ghrelin suppression. Therefore, satiety due to gastric distension would be increased but intestinal satiety signalling to the brain diminished (75).

Collectively, the release and maintenance of episodic signals arising from the GI tract likely have an additive effect in satiation, satiety and the ability to compensate accurately for prior energy intake (51, 76-78). Factors such as the time interval between meals (see Figure 1) will influence the relative contributions of gastric and intestinal signals to appetite control. Gastric distension by food may play a major role in the sensation of fullness whereas the reduction of hunger feelings after a meal result from an interaction of nutrients with receptors in the small intestine (51). Differences in the initial versus subsequent rate of gastric emptying (79) may explain why accuracy in compensation for prior energy intake diminishes as the time interval to the next meal increases (80) - thus highlighting the importance of considering the kinetic and temporal pattern of gastric emptying in relation to

appetite control. The characteristics of the meal (52, 81) (see Figure 1) will also have a role. In the absence of nutrients for example gastric distension appears to be a major factor in the return of hunger (81). Overall, there appears to be an important integrative relationship between gastric emptying and gut peptides in appetite control.

- Figure 1 here -

The efficacy of bariatric surgery in weight loss: what is the role of the emptying rate?

Elucidating the mechanisms behind changes in appetite with surgery is firstly important because such knowledge may facilitate the development and modification of anti-obesity treatments to achieve at least some of the weight loss of surgery (87). Early studies indicated that after gastric bypass solids emptied at a slower rate from the small gastric pouch (88-90). However, there was no correlation with weight loss (88-89) suggesting other mechanisms caused weight loss (88). These studies were cross sectional and comparisons were made either with controls or other surgeries. Although now an abandoned procedure, with jejunoileal bypass (JIB), gastric emptying was slowed 9 months after surgery (91) and unchanged in patients 20 years after JIB compared to controls (92). Today, the most commonly performed bariatric procedures are Roux-en-Y gastric bypass (RYGB), adjustable gastric banding and sleeve gastrectomy (SG) (see (93) for a detailed description of surgical procedures). RYGB, a procedure that both minimizes gastric capacity and accelerates delivery of nutrients to the distal small intestine, produces greater weight loss and earlier resolution of diabetes than gastric banding, which is a purely restrictive procedure (94). Various mechanisms have been proposed to contribute to weight loss and post-surgical reductions in appetite after RYGB (see (87) for a more complete review). There is no doubt that gastric restriction plays a role in weight loss (95). A gastric pouch with a volume of 30ml restricts the amount of food that can be consumed and accommodated following RYGB. However, gastric restriction does not account for the increase in weight loss with RYGB when compared with gastric banding. Evidence suggests that the restrictive and malabsorptive components alone are insufficient to account for the resulting weight loss with RYGB (23). Reduced ghrelin levels after RYGB have also been implicated (24). However, increased, decreased and unchanged fasting ghrelin levels after surgery have been reported (39). Instead, the majority of studies suggest that the efficacy of RYGB in reducing appetite and promoting weight loss may relate predominantly to distal small intestinal effects (95). After gastric bypass the pyloric ‘meter’ or brake is absent and the diversionary component allows rapid transit of nutrients to the jejunum (51). One hypothesis is that the expedited delivery of nutrients to the hindgut may stimulate a faster and enhanced postprandial release of anorexigenic gut peptides (87). The higher levels and early appearance of PYY and GLP-1 are consistent observations following RYGB (69) but not after gastric banding (96) and could explain the difference in weight loss (97). A faster emptying rate from the small pouch has been suggested to contribute to the greater anorexigenic neurohormonal response following RYGB (9, 11-12). Following RYGB, GLP-1 levels about 5 fold higher than observed after

meal ingestion in healthy lean individuals have been reported (12). In this study similar patterns of decreased hunger, increased fullness and a faster delivery of nutrients to the intestine were observed at 3 days, 2 months and 1 year post RYGB (12). At 6 weeks after RYGB compared to pre-surgery, Morinigo et al (11) observed an accelerated emptying of the small pouch, an increased postprandial GLP-1 and PYY release, reduced hunger and increased satiety. In contrast, with gastric banding, the emptying rate is unchanged (98-100).

An accelerated emptying rate has also been observed after SG, a procedure which does not bypass the duodenum, and may contribute to the increased GLP-1 (101) and PYY (13) secretion after SG. Following RYGB and SG inducing similar weight losses, postprandial PYY levels increased which corresponded to an increase in satiety (13). Two possible explanations were proposed: 1) SG changes neuronal or humoral signalling that regulate postprandial PYY secretion, and 2) SG produces a decrease in gastric acid secretion and a faster gastric emptying; both changes which would lead to a faster delivery of undigested nutrients to the intestine and increase the PYY response (13). Studies demonstrating an accelerated gastric emptying following SG in both the initial (10, 101-102) and overall emptying rate (10, 14, 101) support the latter explanation. The duodenal switch procedure has also been associated with accelerated gastric emptying and an increased PYY response (15). Although, it should be noted that the non-operated controls were given a larger meal with a higher energy content in this study. Findings from studies investigating the effects of different surgical procedures on gastric emptying (or emptying of the small pouch in the case of gastric bypass) are summarised in Table 1. Collectively, the evidence indicates that in addition to gastric restriction, bariatric surgery and in particular RYGB and SG reduce weight by changing the profile of circulating gut peptides implicated in appetite control (6-8, 43) which may partially be due to a faster emptying rate and increased delivery of nutrients to the distal small intestine.

- Table 1 here –

Additional surgical and pharmacological weight loss strategies: contrasting effects on gastric emptying

Other surgical methods such as gastric pacing and gastric electrical stimulation which do not alter normal GI anatomy are also being explored as obesity treatments, but to date have produced inconsistent results with amount of weight loss (see (103) for a review). Their exact mechanism of action has not yet been identified; however, changes in gastric emptying have been implicated. Delayed gastric emptying in the initial 45 minutes after eating and reduced food intake was demonstrated with a system of stimulation through temporary fundic mucosal electrodes (104). In contrast, accelerated gastric emptying was observed with the TANTALUS system of stimulation (105); a system found to achieve long term weight loss comparable to gastric banding (106). One

explanation may be that unlike other gastric electrical stimulation devices, the TANTALUS system is activated only following food ingestion.

Both delayed and accelerated gastric emptying has also been implicated in improved appetite control and weight loss in pharmacological studies. The majority of strategies have been directed towards slowing gastric emptying. Initial studies indicated that slower gastric emptying was associated with weight loss after 12 weeks of Sibutramine treatment (107). Recent drug developments have focused on targeting gut peptides such as GLP-1 (exenatide and liraglutide), amylin (pramlintide) and PYY [intranasal PYY (3–36) and AC-162325], which have been demonstrated to slow gastric emptying and reduce appetite and food intake (108-116). In contrast, findings of slowed gastric emptying with the cannabinoid dronabinol led to speculation that faster gastric emptying and enhanced satiation may be one mechanism behind the appetite and weight reducing effects of Rimonabant; a cannabinoid antagonist (117). Torra et al (118) provided the first evidence supporting the hypothesis that pharmacologically accelerating gastric emptying could enhance satiation and reduce meal size. Erythromycin administration in obese individuals exerted a faster gastric emptying in the first 15 minutes after initiation of eating which translated into a small reduction in energy intake (135 kcal) compared to individuals who received placebo. However, the most commonly studied prokinetic drugs including erythromycin, metoclopramide, domperidone and cisapride have side effects such as nausea (119, 120), making it difficult to separate their effects on appetite. Furthermore, the neurotransmitter systems affected by drugs do not exclusively affect appetite. Another explanation for contradictory findings of both delayed and accelerated gastric emptying being implicated in reduced appetite and energy intake may be that some pharmacological approaches can interfere with or override the endogenous release of gut peptides implicated in appetite control such as CCK (121-122), GLP-1 (122-123) and PYY (115, 122). For example delayed gastric emptying caused by exendin-4 may cause duodenal nutrient delivery to decrease to such an extent that little endogenous GLP-1 is released (123). Furthermore, a drug-induced delay in gastric emptying results in reduced ghrelin suppression (74). These effects are much different to the normal physiological regulation of food intake whereby the endogenous release of various peptides and suppression of ghrelin play a key role in appetite control. As a result it is difficult to apply findings from pharmacological studies manipulating gastric emptying to strategies such as lifestyle interventions.

Summary of effects of surgical and pharmacological weight loss strategies on gastric emptying

The majority of recent gastric bypass and SG studies have been found to accelerate the emptying rate, while gastric banding appears not to alter gastric emptying. Other surgical interventions and pharmacological strategies targeting appetite control have been demonstrated to both accelerate and delay gastric emptying. The ability of these varied strategies to reduce appetite and promote weight loss while having opposite effects of gastric emptying could suggest that modulation of gastric emptying may only have a minor role in weight loss. However, these contrasting findings could also

be attributed to differences between interventions and methodologies. Overall, when accounting for methodological differences and the emerging evidence from gastric bypass and SG studies in particular, the literature reviewed suggests that other strategies which accelerate gastric emptying and the delivery of nutrients to the distal small intestine may stimulate an earlier and enhanced endogenous release of anorexigenic gut peptides and improve appetite control.

Lifestyle Interventions, gastric emptying and gut peptides

Understanding the effects of energy restriction and exercise-induced energy deficits on GI targets of appetite control may be important for tailoring lifestyle interventions to minimise the impact of weight loss on appetite in future. Studies that have measured the effects of lifestyle interventions on gastric emptying and on both fasting and postprandial gut peptide responses are summarised in Tables 2 and 3 respectively.

- Tables 2 and 3 here -

Energy restriction

There is some evidence that energy restriction is associated with a slower gastric emptying. Patients with anorexia nervosa experience delayed gastric emptying (141-144), which returns to typical rates when re-fed (142-143). After a 4-day fast, gastric emptying of a glucose drink was slower in lean and obese subjects (126). Postprandial PYY also decreased after 4 days of a 25% energy restriction (134). The few studies which have examined the effects of energy restriction-induced weight loss on gastric emptying have also indicated a slower emptying (124-125, 131), although some report no change (127, 132). Four months of energy restriction and marked weight loss resulted in slower gastric emptying in 20 morbidly obese individuals (125). Following 16 weeks of dietary intervention achieving a mean weight loss of 18.8kg and a further 8 weeks of weight stabilisation, gastric emptying was slowed during the initial 30 minutes but the overall emptying rate was unaffected in 19 obese subjects (124). The authors suggested that this slowing of the initial emptying rate might postpone meal-termination and thereby pre-dispose to overconsumption and regain of a weight loss. This contention is supported by evidence that energy restriction-induced weight loss is associated with a blunted postprandial release of PYY and GLP-1 after a solid meal (135, 137). Following a 10kg weight loss induced by energy restriction or RYGB, postprandial PYY (22) and GLP-1 (25) levels during an oral glucose tolerance test were increased after surgery compared to no change after energy restriction. This could partially explain the relative efficacy of RYGB compared with energy restriction

in weight loss. The authors speculated this may be due to a more rapid delivery of nutrients to the intestine after gastric bypass. One explanation for findings of unchanged postprandial PYY and GLP-1 levels after energy restriction in these studies (22, 25) is the use of a low-energy liquid meal. With regard to CCK, no significant differences in fasting or postprandial CCK concentrations following diet induced weight loss have been observed (26, 145), although peak values occurred 30 minutes later following 8 weeks of energy restriction, suggesting that pancreatic or gastric and intestinal functions might have changed to cause this shift (26).

While further studies are needed, these findings collectively suggest that an energy deficit induced by energy restriction may delay and/or reduce the release of postprandial gut peptides involved in the episodic control of appetite, possibly mediated by a slower delivery of nutrients to the intestine. These changes could contribute to reduced appetite control and hence be a contributing factor to the relative lack of efficacy of energy restriction in long term weight loss and maintenance.

Exercise

The effects of an exercise-induced energy deficit on gastrointestinal mechanisms of appetite control and gastric emptying in particular have received little investigation. Instead, as gastric emptying plays a major role in the availability of ingested drinks during exercise (146), research has focused on determining the optimal properties of sports drinks to enhance performance. In general, the evidence clearly supports a delay in gastric emptying during strenuous exercise (147-153), and although there is some disparity (154-155), there is an acceleration in gastric emptying during mild to moderate exercise (150, 156-157). Few studies have examined the effects of short term exercise on gastric emptying. Therefore, although the role of gastric emptying in appetite regulation is well understood, the influence of exercise is not. Any adaptations in gastric emptying that occur due to exercise could influence the compensatory responses in energy intake. One study reported no significant change in gastric emptying after a moderate intensity 7 week intervention in adolescent girls compared to a control group (130), but no significant weight loss was observed with exercise. The effect of exercise-induced weight loss on gastric emptying is unknown. Nevertheless, changes in postprandial gut peptide levels (see Table 3) and appetite (41) have been observed following exercise interventions with and without weight loss suggesting exercise may also influence gastric emptying independent of weight loss or energy balance.

In terms of chronic adaptation to regular exercise (and hence potentially an influence on appetite in weight maintenance), two cross sectional studies provide limited evidence that gastric emptying is faster in habitually active individuals. Faster gastric emptying was reported in marathon runners compared to sedentary individuals (129) and in a small sample of elderly active compared to inactive individuals (128). In a cross sectional study of 20 men representing a wide range of daily

physical activity levels, energy and nutrient intakes increasing energy intake was significantly correlated with faster orocecal transit time (OCTT) (158). Although it was suggested that the high energy intake associated with chronic exercise may be associated with significant gastrointestinal adaptations (i.e. accelerated OCTT), it could also be speculated that increased physical activity levels may have led to faster OCTT, and thus higher caloric intakes as a result of a shorter satiety period. The causal nature of this relationship may be critical to understanding the long term effects of exercise on energy intake. A high-fat diet-induced increase in gastric emptying is associated with diminished sensitivity to the appetite suppressing effects of gut peptides (for a review, see (159)) as central nervous system sensitivity to peripheral signals is reduced (18). Therefore, it is possible that faster gastric emptying in chronic exercisers may reflect an adaptation to a higher energy intake and be similarly associated with diminished sensitivity to the appetite suppressing effects of episodic gut peptides. However, given consistent evidence of improved appetite control in chronic exercisers (160-161), the following hypothetical model outlines one possible mechanism contributing to the efficacy of exercise in weight maintenance (Figure 2). Further, it identifies one mechanism to explain why activity-induced energy expenditure could mediate the inverse relationship between meal frequency and adiposity, despite a higher energy intake (162).

- Figure 2 here -

Collectively, while the limited evidence suggests chronic exercisers have a faster gastric emptying, further studies are needed to determine the temporal patterns of changes in gastric emptying with exercise programmes and with exercise induced weight loss.

Combining energy restriction and exercise

A common method of improving weight loss is to combine energy restriction with exercise training. Findings from studies which have investigated the effects of combined exercise and dietary intervention on gut physiology are not conclusive, mainly due to differences in how the diet was manipulated and the volume of exercise employed. Varying degrees of weight loss have been observed, along with differing effects on appetite and gut peptides (see Table 3). Gastric emptying was unchanged after both 4 and 8 weeks of energy restriction combined with exercise advice but the overall emptying rate was delayed after 1 year of the same intervention (131). Following a combination of a reduced-fat energy-restricted diet and 12 weeks of exercise intervention, the PYY response was increased (31). In contrast, when energy restriction was combined with 180min/week of exercise, the PYY response decreased (13). The effects of different combinations of diet and exercise manipulations on gastrointestinal mechanisms of appetite control warrant further investigation.

Methodological Issues: comparing the effects of different strategies

The literature reviewed highlights a number of important methodological issues. It is worth noting that the effects of different strategies on GI targets could vary depending on the magnitude of weight loss. Further, the effects may vary temporally – that is, acute changes may differ from chronic changes. It is critical to determine whether alterations in GI function occur in response to weight loss or the treatment strategy *per se* and to distinguish between changes in fasting and postprandial and exogenous and endogenous levels of peptides. While bariatric surgery may be used as a model to understand physiological weight loss (39), the mechanisms influencing the emptying rate after surgery may be different to those that influence gastric emptying after other interventions. This review has considered the effects of different strategies on gut peptides as currently measured in the systemic circulation. However, peripheral plasma levels may not necessarily reflect the local effects of gut peptides as they may also exert their action by paracrine or neurocrine routes (163-164). As a result the measurement of subjective appetite sensations should not be undervalued as increases or decreases of endogenous plasma levels, particularly of a peptide measured in isolation, may not translate to changes in hunger or fullness. However, subjective appetite sensations are not reported in many studies (9, 13, 15, 22, 24-26, 31, 101-102, 127, 137-138), and when they are reported the measures vary. The behavioural expression of appetite being measured (e.g. meal size, meal frequency) should also be considered. Similarly, the gastric emptying parameters and methods used need to be taken into account as there may be no relationship between the initial (i.e., lag phase) and overall emptying (165). Although beyond the scope of the current review, in addition to gastric emptying, the efficiency of intestinal absorption (determined by factors such as the viscosity and structure of the meal (see (166)) will influence the release of gut peptides. A liquid meal for example, despite a faster gastric emptying, may be absorbed entirely in the duodenum and not reach the lower part of the ileum to directly stimulate L cells (25, 167). Collectively, these methodological issues are important to acknowledge as they may have different implications for appetite control.

Future Directions: GI targets of appetite control for weight loss

A large percentage of weight loss with Roux-en-Y gastric bypass could be attributed to the associated neuroendocrine changes (23). Dietary, pharmacological and surgical strategies attempting to mimic the effects of bariatric surgery on GI responses are likely to be an ongoing area of intense research. The focus of pharmacological strategies may centre on gut peptides and their receptors (168), developing long acting peptides (43) and combination strategies of long acting adiposity signals with short term episodic signals as has recently been shown to be effective with a combination of pramlinitide and metreleptin (16). Others are working to identify a drug that accelerates gastric emptying when administered orally to limit meal size (169). The major issue related to dietary

manipulations using functional foods is how to minimise the increase in hunger while maintaining an energy deficit (170). The development of novel foods targeting G protein-coupled receptors (171) and foods designed to reach the distal small intestine earlier and so stimulate an earlier and enhanced postprandial release of PYY and GLP-1 may counteract the blunted response of these gut peptides to energy restriction. Doucet and Cameron (2007) (45) proposed that offering low calorie snacks specifically designed to elicit maximal post snack PYY and GLP-1 levels to coincide with main courses could lead to better dietary control and compliance. However, the same group recently reported the timing of a high protein preload had no effect on PYY, GLP-1 or energy intake (172).

Currently, there is limited evidence concerning the effects of exercise on GI mechanisms of appetite control and weight loss. Exercise is universally available and has the added attraction of many additional health benefits (173) including weight maintenance (174). One hypothesis by which exercise facilitates weight maintenance, based on the early work of Mayer (175) is that exercise alters sensitivity to episodic hunger and fullness signals (160-161, 176) through an increase in postprandial satiety signalling driven by changes in gut peptides (30, 41, 177). Faster gastric emptying may have a role in improved appetite control with chronic exercise as hypothesised in this review. However, this is based on limited cross sectional evidence; therefore integrative studies of gastrointestinal responses are vital. Changes in gastric emptying that result from exercise interventions designed to assess the efficacy of exercise for weight loss should also be examined as they may not be identical to chronic adaptations that occur in habitual exercisers over longer periods of time. Short term evidence suggests exercise-induced energy expenditure (EE) and energy intake (EI) are only weakly coupled (178-179).

A further issue is whether it would be possible to structure a combination of dietary and exercise regimes to favourably alter gastric emptying and endogenous levels of peptides in such a way that the effects of weight loss on appetite and other compensatory mechanisms could be minimised. The independent and combined effects of dietary manipulations and exercise are important. For example, a high-fat diet may undermine any potential beneficial effects of exercise on GI mechanisms of appetite control. It is possible that in some people exercise increases the selection of high-fat energy dense foods (4), which could therefore contribute to the large inter-individual variability observed in weight loss response to exercise (180). In contrast, individuals successful at losing weight with a 12 week intensive exercise intervention increased their fruit and vegetable intake (181). Chaput et al (2007) (182) demonstrated that using a combination of exercise with a diet designed to maximise satiation, significant weight loss could be achieved, indicating that the combination of a healthy satiating diet and exercise allows the achievement of metabolic benefits while potentially avoiding body weight relapse. GI mechanisms were not measured in these studies. Future studies investigating the individual effects of different manipulations of diet and exercise on gastric emptying and gut peptides along with different temporal combinations will advance the understanding of manipulating these lifestyle factors for better use in both weight loss and maintenance.

GI targets of appetite control: part of an integrated process

Changes in the expression of appetite influenced by gastric emptying may be expressed behaviourally as changes in meal size, meal frequency and snacking behaviour between meals. Increasing post-ingestive negative feedback (e.g., anorexigenic gut peptides) has been emphasised as one optimal therapeutic goal in the treatment of obesity (183). Strategies which accelerate gastric emptying represent a reasonable target for preventing overconsumption by increasing the release of anorexigenic gut peptides. However, an overall faster gastric emptying time, despite potentially enhancing the magnitude of satiety sensations from intestinal factors between meals is likely to lead to decreased feelings of fullness arising from the stomach and shorten the interval to the onset of the next meal. Thus meal frequency may be increased and hence net energy intake may not be reduced (118). For weight loss, the most effective strategy to reduce energy intake will be one that targets satiation, satiety and snacking behaviour by manipulating the emptying rate to maximise both the sensation of fullness from the stomach, and the early onset and prolonged release of gut peptides from the intestine.

The concept that appetite may be consciously overridden in the short-term but this is superseded in the longer term by a biologically determined set-point has been proposed as one mechanism by which lifestyle interventions fail to sustain weight loss (43). As there is a strong volitional control over eating behaviour, psychological influences should not be undervalued (184). Reward pathways, stress, social values, diurnal rhythm, learned behaviours and eating behaviour related traits (e.g. dietary restraint) could have a strong influence on food intake. The resulting eating patterns may be influenced by and also contribute to alterations in gut physiology. Following RYGB, the ‘supra-normal’ nutrient stimulated gut peptide response (12, 96-97, 185) may override both homeostatic defences of body weight and non-homeostatic factors influencing food intake. Changes in gastric emptying and gut peptides induced by lifestyle interventions are unlikely to be of the same magnitude as those following surgery - other factors such as the hedonic response to foods could over-ride signals from the GI tract (186). While developing a strategy to target the GI tract to maximise satiation and satiety may have a critical role in facilitating weight loss with lifestyle strategies, the greatest weight loss will be achieved by adopting a multidisciplinary approach.

Conclusions

A key factor in the long term success of a weight loss intervention is to minimise the impact of weight loss on compensatory responses including energy intake. The complexity of appetite control should not be limited to gastric emptying and gut peptides but their measurement becomes essential to understand the mechanisms by which weight loss strategies may act to increase or decrease appetite and food intake and thus influence weight regain. This review demonstrates that different strategies exert diverse postprandial effects. The existing literature is still limited and the study designs vary in the methods used and parameters reported. Relative to lifestyle interventions, surgical interventions

produce greater short and long term weight loss which may be explained by changes in appetite. From the evidence so far it is likely that in addition to gastric restriction, gut peptides play a key role in the improved appetite control experienced by those who undergo surgical procedures such as sleeve gastrectomy and Roux-en-Y gastric bypass. Although findings remain associative, this response may be due in part to an accelerated delivery of nutrients to the distal small intestine. A better understanding of how lifestyle interventions such as diet and exercise affect gastrointestinal targets of appetite control and the associated implications for food intake is urgently needed to facilitate their more effective use in weight management and so combat the current obesity epidemic on a population level.

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Figure 1. A hypothetical model of the relative contributions of gastric distension, cholecystokinin (CCK), glucagon-like peptide-1 (GLP-1), peptide YY (PYY) and ghrelin (all episodic signals influenced by gastric emptying) to satiation and satiety.

Figure 2. A model to describe how chronic physical activity could potentially impact on gastric emptying, appetite regulation and energy balance

Table 1 A summary of studies examining the effects of bariatric surgeries on gastric emptying

Procedure	Reference	Weight Loss*	Study design/intervention	Initial GE (outcome)	Overall GE (outcome)
Gastric Bypass	Horowitz et al. (1982) (89)	23 ± 3kg	Cross section of patients (n = 12) 12 months after bypass compared to non-operated controls (n = 11)	faster liquid (t_{lag}, % remaining at 5min, 10min), solid slower except faster in 4 subjects(t_{lag})	faster liquid ($t_{1/2}$). solid slower except faster in 4 subjects ($t_{1/2}$, % remaining at 50, 100min)
Jejunoileal Bypass	Näslund et al. (1997) (92)	44 ± 4 to 31 ± 4 kg/m^2	Cross section of JIB operated subjects 20 +/- 3 yrs ago (n = 7) compared to non-operated obese controls (n = 7)	unchanged (t_{lag})	unchanged ($t_{1/2}$, % remaining at 60, 90, 120 min)
	Näslund et al. (1998) (91)	42 ± 4 to 31 ± 4 kg/m^2	GE measured pre and 9 months post surgery (n = 9)	slower (t_{lag})	slower ($t_{1/2}$)
Roux-en-Y Gastric Bypass	Morignio et al. (2006) (11)	15.4 ± 6.3kg	GE measured pre and 6 weeks post RYGB (n = 9)	faster (AUC_{0-60})	faster (AUC_{0-60})
	Akkary et al. (2008) (9)	50.6kg weight loss in those with faster initial GE compared to 47.3kg in those with slower	Comparison of weight loss in those with slower (n = 116) and faster initial (n = 188) emptying at 1 day postoperative at 1 year follow up	faster initial GE (30min) 1 day postoperatively associated with greater weight loss at 1 year	-
	Falkén et al. (2011) (12)	45.5 ± 1.9 (preoperative) to 38.6 ± 1.8 (at 2 months) to 30.3 ± 1.8 (at 1 year) kg/m^2 .	GE measured pre and 3 days, 2 months and 1 yr post RYGB (n = 12)	Faster (acetaminophen absorption peak time)	Faster (acetaminophen absorption $t_{1/2}$)
Sleeve Gastrectomy	Shah et al. (2010) (14)	-	Cross section of morbidly obese non operated type 2 diabetics (n = 20), morbidly obese type 2 diabetics operated with SG (n = 23), lean controls (n = 24)	-	faster ($t_{1/2}$) in operated
	Melissas (2008) (10)	Mean group weight: 140 (preoperative) to 101 (at 6 months) to 89 (at 24 months) kg.	GE measured pre surgery, 6 and 24 months after SG (n = 9)	faster (t_{lag}) at 6 and 24months compared to pre-surgery	faster ($t_{1/2}$, % GE rate) at 6 and 24months compared to pre-surgery
	Braghetto et al (2009) (101)	-	Cross section of obese subjects 3 months after SG (n = 20) compared to normal controls (n = 18)	faster (% remaining at 20, 30, 60 min) in operated	faster ($t_{1/2}$) in operated

	Bernstine et al. (2009) (102)	125 ± 25 to 99 ± 22 kg	GE measured pre surgery and 3 months post SG (n = 21)	faster (% remaining at 30min)	unchanged ($t_{1/2}$, % remaining at 1,2,3,4h)
Gastric Banding	de Jong et al. (2008) (98)	47.8 to 41.7 kg/m^2	GE measured pre surgery and 16 months post gastric banding (n = 16)	unchanged (t_{lag})	unchanged (GE rate (%/h))
	Burton et al. (2010) (99)	143.3 ± 25.5 to 96.3 ± 18.2 kg	Cross over design. 2 GE studies: One with the LAGB at its optimal volume and another with 1 ml within the LAGB (n = 14 patients who had achieved >50% weight loss > 12 months post surgery).	not tested	unchanged ($t_{1/2}$)
	Usinger et al. (2011) (100)	125 ± 8 to 121 ± 8 kg	GE measured pre and 6 weeks post LAGB (n = 8 obese with and without impaired glucose tolerance).	unchanged (acetaminophen absorption peak time)	unchanged (acetaminophen absorption AUC).
BPD-DS	Hedberg et al. (2011) (15)	51.7 to 31.1 kg/m^2	20 patients having undergone BPD-DS in median 3.5 yrs previously compared to previous normal GE data in the same lab	faster (t_{lag}) in operated	faster ($t_{1/2}$) in operated

* Weight Loss in units reported in original paper. AUC: area under curve; BPDS: biliopancreatic diversion with duodenal switch; GE: gastric emptying; LAGB: laparoscopic gastric band; JIB: Jejunoileal bypass; SG: sleeve gastrectomy; $t_{lag:}$ lag time; $t_{1/2:}$ half time.

Table 2 A summary of studies examining the effects of lifestyle interventions on gastric emptying

Lifestyle Factor	Reference	Weight Loss*	Study design/intervention	Initial GE (outcome)	Overall GE (outcome)
Diet	Verdich et al. (2000) (124)	18.8kg, 14.8%	8 wks formula (4.2 MJ p/d), 8 wks restriction (6.3 MJ p/d) followed by 8 wks weight maintenance (n = 19 obese)	slower (t_{lag})	unchanged (total 4h emptying time)
	Tosetti et al. (1996) (125)	10%	parallel study of 4 month energy restriction with or without intragastric balloon (n = 20 obese)	slower	slower (overall emptying rate)
	Corvilain et al. (1995) (126)	-	GE measured after 12hour and 4day fast (n = 12 normal weight, n = 11 obese)	faster (t_{lag})	slower ($t_{1/2,}$ in both groups)
	Hutson et al. (1993) (127)	13.7kg, 8.3%,	3-4 wks of a 100kcal p/d diet. GE tested 2 days after the normal diet had been reinstituted (n = 8 obese)	unchanged (t_{lag})	unchanged ($t_{1/2}$)
Exercise	Shimamoto et al. (2002) (128)	-	cross section of active (n = 7) and inactive (n = 7) elderly individuals	faster in active (time of peak $^{13}CO_2$ concentration)	faster in active (time of peak $^{13}CO_2$ concentration)
	Carrio et al. (1989) (129)	-	cross section of marathon runners (n = 9) and sedentary (n = 9) males	faster in marathon runners (t_{lag})	faster in marathon runners ($t_{1/2}$)
	Horner et al. (2010) (130)	↔	intervention of 3x40 min moderate intensity exercise classes p/wk (n = 9 adolescent girls) compared to a control group (n = 10).	unchanged (t_{lag}, t_{lat})	unchanged ($t_{1/2}$, t_{asc})
Combined Diet and Exercise	Mathus Vliegen et al. (2006) (131)	10.4kg, 9.9%	1 year of daily energy deficit of 2.3MJ (an energy- and fat-restricted diet), exercise (advice on increasing leisure activity and optional aerobics classes), behavioral modification and placebo tablets (n = 9)	unchanged (t_{lag})	slower (emptying rate (%/h)), unchanged ($t_{1/2}$)
	Mathus Vliegen et al. (2006)	3.5kg	2 months of same intervention above (n = 14)	unchanged (t_{lag})	unchanged ($t_{1/2}$), (%/h)
	Mathus Vliegen et al. (2006)	2.3kg	4 weeks of same intervention above (n = 42)	unchanged (t_{lag})	unchanged ($t_{1/2}$), (%/h)
	Wright et al. (1983) (132)	-	undefined intervention - subjects who lost weight during the 18 month study period underwent a second GE test (n = 4 obese)	unchanged (% remaining in the stomach)	unchanged ($t_{1/2,}$ % remaining in the stomach)

* Weight Loss in units reported in original paper. GE: gastric emptying; t_{lat}: latency time; $t_{asc:}$ ascension time $t_{lag:}$ lag time; $t_{1/2:}$ half time.

Table 3 A summary of studies examining the effects of lifestyle interventions on fasting and postprandial appetite gut peptides

Lifestyle Factor	Reference	Weight Loss*	Study design/intervention	Fasting gut peptides	Postprandial gut peptides
Diet	Verdich et al. (2001) (133)	18.8kg, 14.8%	pre and post 8 wks formula (4.2 MJ p/d), 8 wks restriction (6.3 MJ p/d) followed by 8 wks weight maintenance (n = 19 obese)	GIP ↓, GLP-1 ↔	GIP ↓, GLP-1 ↑
	Cummings et al. (2002) (24)	17.3kg, 17.4%,	3 months diet-induced weight loss followed by 3 months maintenance at reduced weight (n = 13 obese)	ghrelin ↑	ghrelin ↑
	Doucet et al. (2004) (134)	-	4 day energy restriction of 25% energy intake	PYY ↓	PYY ↓
	Adam et al. (2005) (135)	6.1kg	pre and post 6 wk very low energy diet (n = 32 obese)	GLP-1 ↔ (trend to ↓),	GLP-1 ↓,
	Moran et al. (2007) (136)	4.2 ± 3.9kg	pre and post 8 wks energy restriction (deficit of ~ 30%, intake), (n = 14 with PCOS, n = 14 controls)	ghrelin, PYY, CCK ↔	PYY, CCK, ghrelin ↔
	Lafferere et al. (2008) (25)	9.8kg	pre and post 55 +/- 9.9 days energy restriction (1000 kcal/d meal replacement plan) (n = 10 obese)	GIP ↔, GLP-1 ↔	GIP ↔, GLP-1 ↔
	Chearskul et al. (2008) (26)	17.9kg, 15%,	pre and post 8wks after restriction of approx 1800kj/d and 1 week of maintenance (n = 12 obese)	CCK ↔	CCK ↓ (30min)
	Olivan et al. (2009) (22)	10kg	Pre and post meal replacement plan 1000 kcal p/d. Post measurements after 10kg weight loss (55.0 ± 9.9 days) (n = 10 obese)	ghrelin ↑, PYY ↔	PYY ↔, ghrelin ↔
	Essah et al. (2010) (137)	5.8kg (LF), 1.0kg (LCHO)	Pre and post 8 wks energy restricted (-500kcal p/d) low fat (LF) or low CHO diet (LCHO) (n = 30 obese)	PYY ↓(following both diets)	PYY ↓(following both diets)
Exercise	Chanoine et al. (2008) (138)	↔	Pre and post 1h p/d aerobic exercise 65-75%HRmax) for 5 days, (n = 34 normal and overweight adolescent boys)	GLP-1 ↔	GLP-1 ↑ (30 min)
	MacKelvie et al. (2007) (139)	↔	Pre and post 1h p/d aerobic exercise (65-75%HRmax) for 5 days, (n = 34 normal and overweight adolescent boys)	total ghrelin ↔, AG ↑, DG ↔	total ghrelin ↔, AG ↑, DG (in normal weight) ↓, DG (in overweight) ↑

	Hurley et al. (1991) (140)	↔	Pre and post 10 wk exercise intervention (20 min at 70% VO_2max 3d p/wk) (n = 7 normal weight sedentary)	PP slight ↑, GIP ↔	PP slight ↑, GIP ↔
	Martins et al. (2010) (30)	3.5kg	Pre and post 12 wk aerobic exercise intervention, (5 d p/wk, 500kcal at 75% HR max) (n = 15 overweight)	AG ↑, total ghrelin, GLP-1, PYY ↔	↑ AG suppression, ↑ GLP-1, PYY ↔
	Kelly et al. (2009) (31)	2.8 ± 0.5 kg.	Pre and post 12 wk exercise (5d p/wk at 75%VO_2max) intervention combined with a eucaloric diet (n = 10)	PYY ↔, GIP ↔	PYY↑ (0-30min), GIP ↔
Combined Diet and Exercise	Valderas et al. (2010) (13)	16.6 ± 4%	Pre and post a 2month low-calorie diet (1300–1800 kcal/d (20–25 kcal/kg of ideal weight)), behavioral modification and 180 min/wk of aerobic and resistance exercise (n = 8 obese)	PYY ↓	PYY ↓
	Kelly et al. (2009) (31)	8.3 ± 1.1kg	Pre and post 12 wk exercise intervention (5d p/wk at 75%VO2max) combined with a hypocaloric diet. Diet reduced ~700kcal fewer daily, reduced fat intake by 5% (n = 9 obese).	PYY ↔, GIP ↔	PYY↑ (0-30min), GIP ↓
	Leidy et al. (2007) (38)	2.5 ± 0.9kg	Pre and post 13 wk exercise intervention (5 d p/wk at 70-80% HRmax) combined with energy restriction to achieve -30-60% energy deficit, (measured ghrelin profiles over 24h) (n = 8 normal weight)	ghrelin ↑	ghrelin ↓
	Mathus Vliegen et al. (2006) (131)	2.3 (at 1wk) to 10.4 (at 1 year) kg.	Pre and at 4 wks, 8 wks and 1 yr. 1 yr intervention of energy restriction (an energy- and fat-restricted diet), exercise (advice on increasing leisure activity and optional aerobics classes), behavioral modification and placebo tablets (n = 9 obese)	CCK ↔ (at all time points)	CCK ↔ (at all time points but trend to ↓ at 4 weeks)

* Weight Loss in units reported in original paper. AG: acylated ghrelin; DG: deacyl ghrelin; CCK: cholecystokinin; CHO: carbohydrate; GIP: gastric inhibitory polypeptide; GLP-1: glucagon-like peptide-1 PCOS: polycystic ovarian syndrome; PP: pancreatic polypeptide; PYY: peptide YY; HRmax: maximum heart rate; VO_2max: maximal oxygen uptake

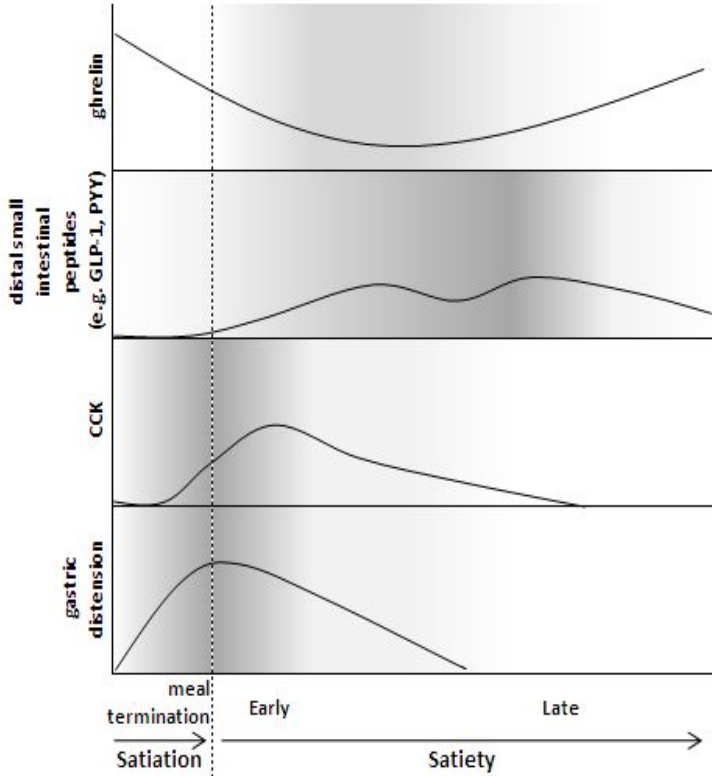

Figure 1. A hypothetical model of the relative contributions of gastric distension, cholecystokinin (CCK), glucagon-like peptide-1 (GLP-1), peptide YY (PYY) and ghrelin (all episodic signals influenced by gastric emptying) to satiation and satiety. Darker shading indicates a greater relative contribution. Time (x axis) and magnitude (y axis) are dependent on the meal characteristics. Gut peptides are particularly sensitive to specific macronutrients (e.g. CCK to fat and protein (82); GLP-1 to carbohydrate and fat (85); PYY primarily to fat (85); ghrelin suppression to protein and carbohydrate (83)) and peak at different time points. Ghrelin is the only peptide implicated in meal initiation, rising before a meal and falling approximately 60min after a meal (35). During a meal and shortly after, gastric distension and CCK (peaking within 15min (84)) are important determinants of satiation. The release of GLP-1 and PYY occurs in a biphasic pattern and can remain elevated for hours after a meal (59, 86). As the stomach continues to empty, it is likely that the exposure of nutrients to the distal small intestine has an increasingly greater contribution to satiety. These episodic signals may also be modulated by tonic signals such as leptin and insulin which are responsive to energy availability and body adiposity.

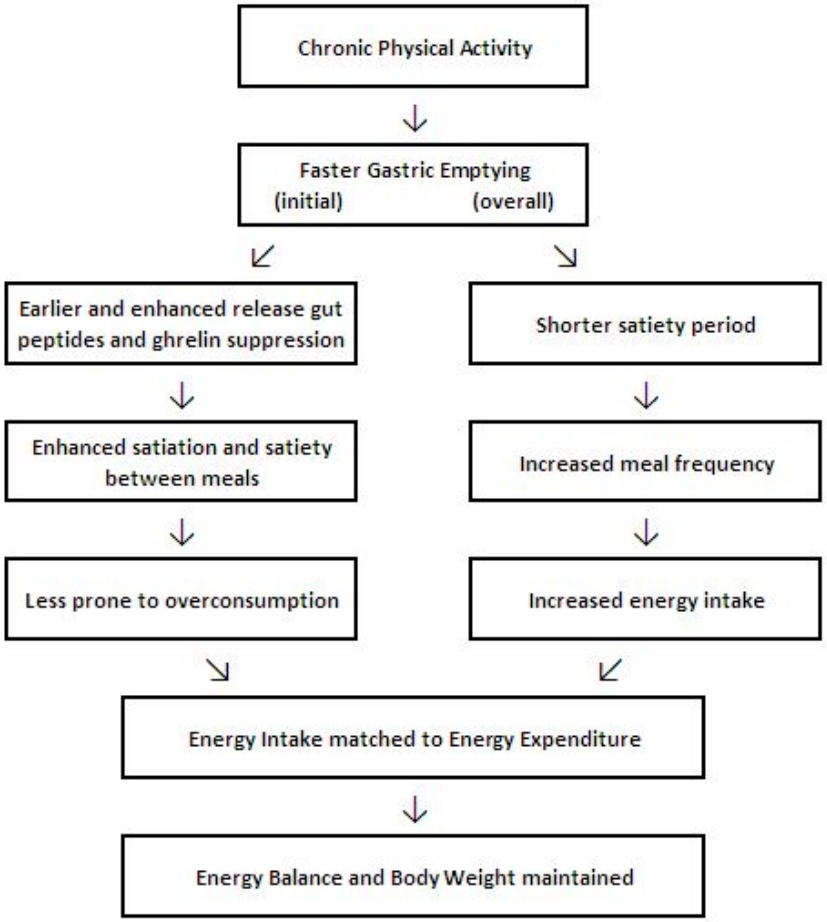

Figure 2. A model to describe how chronic physical activity could potentially impact on gastric emptying, appetite regulation and energy balance