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Review Article

Bariatric endoscopy: Keep it simple and smart

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A B S T R A C T

Although not yet fully elucidated, the science behind the mechanisms of energy homeostasis has advanced significantly in recent decades. Current treatment paradigms, however, have not taken advantage of this evolving body of knowledge. The use of the scalpel to treat obesity is historically rooted in society's perception of obesity as the result of inadequate willpower—and not a "disease." It is an individual's choice to eat excessively that leads to obesity and not a disease state to which the individual has fallen victim. Hence, to lose weight, the patient's anatomy must be surgically altered to either restrict nutrient intake or absorption. Endoscopic treatments have been modeled after this surgical paradigm. It is time for a new paradigm and the development of endoscopic treatments that apply our current understanding of the physiological mechanisms that control energy homeostasis. The author reviews the relevant aspects of the new science and offers a new treatment paradigm that is both simple and smart. A duodenal insert that slows the passage of ingesta through the proximal small bowel is described. The device triggers both early satiation and a continuing sense of fullness to assist in the reduction of caloric intake.

Keywords: Cholecystokinine, Duodenal implant, Endoscopic treatment, Obesity, Satiation

Introduction

Worldwide obesity rates are staggering. According to the Centers for Disease Control, obesity rates have increased so dramatically that today more than two-thirds of Americans (approximately 200 million adults) are overweight or obese. Upward of $240 billion is spent each year by the United States healthcare system on obesity and its comorbidities.[1] The World Health Organization reports that more than 1.4 billion people worldwide are overweight or obese. Mexico has recently surpassed the United States in terms of the percentage of the population that is obese. Sadly, more people die today as a result of obesity-related problems than from hunger and malnutrition.

Endoscopic treatment of obesity and metabolic disease is attractive because it fills a therapeutic gap between medical therapy and surgery. The inherent advantages are the lesser invasive peroral approach and lower cost. In addition, endoscopic techniques are applicable across a continuum of obesity and metabolic disease. To date, endoscopic treatments have attempted to mimic the method of action used by the various surgical approaches: restriction, bypass, or some combination thereof. However, challenges exist at multiple levels: (1) the complexity of device technology, resulting in difficult delivery requiring long procedure times, in addition to the specialized training and expertise required; (2) safety profile; and (3) efficacy and durability. What is needed are new paradigms of treatment that keep endoscopic treatment simple and smart, derived from an understanding of the physiological triggers behind obesity and metabolic disease, rather than the surgical paradigm of simply restricting or diverting food intake.

The "surgical" paradigm in endoscopic approaches

The "surgical" paradigm for the treatment of obesity consists of approaches that restrict and/or bypass the normal passage of alimentation in the gastrointestinal tract. Restrictive operations consist of either a reduction in the size of the stomach (e.g., sleeve gastrectomy) or narrowing of the stomach inlet (lap band procedure). Bypass operations divert food from contact with the small bowel (e.g., jejunoileal bypass). The gastric bypass and duodenal switch operations combine restrictive and bypass approaches.

Endoscopic treatments are modeled after the surgical paradigm. The gastric balloon, the first antiobesity treatment introduced in the 1980s, mimics a restrictive operation by occupying space in the stomach. With the development of novel technologies that enable endoscopic suturing and stapling, endoscopists are able to reduce the size of the stomach, similar to a sleeve gastrectomy, or restrict the stomach inlet, similar to a lap band.[1] Endoscopic devices that incorporate sleeves that prevent contact of nutrition with the small bowel mimic a surgical bypass. Sleeves available in some countries today range from 60 cm to 90 cm in length, anchor with barbs proximally in either the bulb of the duodenum or the cardia and extend to the distal jejunum.

These and other endoscopic platforms use complex tools and methods that can have multiple downsides. A high level of

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technical skill is required for delivery and removal requiring specialized training. Procedure times can be long—often in the multiples of standard therapeutic procedures such as polypectomy—and unpredictable, further complicating patient scheduling. Postprocedural pain and intolerance may necessitate considerable inpatient and outpatient management.

The surgical paradigm: flawed and antiquated?

The treatment of obesity with the surgical paradigm is certainly not intuitive. Unlike a tumor or inflamed organ, the "disease" cannot be excised with the scalpel. What then is the genesis of the surgical paradigm? The use of the scalpel to treat obesity is historically rooted in society's perception of obesity as a problem of willpower—and not a disease. It is an individual's choice to eat excessively that leads to obesity and not a disease state to which the individual has fallen victim. Hence, to lose weight, the individual must be forced to either eat less or absorb less. Not surprisingly, a restrictive operation that reduces the size of the stomach to the size of an egg can very effectively force a person to eat less. Or, bypassing the small intestine (where food absorption occurs) can very effectively force a person to absorb less.

Whether done surgically or endoscopically, the surgical paradigm is rooted in negative conditioning. Eating too fast or too much triggers symptoms of discomfort, nausea and vomiting, and altered bowel habits (diarrhea, frequency, flatulence) that discourage further eating. Obviously, such adverse symptoms take a substantial toll on quality of life, and have a negative impact on social interactions that revolve around eating. Consequently, negative conditioning strategies often fail over time because of behavior changes that minimize the negative symptoms (e.g., consumption of high-calorie slurries). In addition, there is compensatory adaptation such as stretching of the stomach after gastric reduction.

Satiation, satiety, and the "gut–brain" axis

The body achieves energy homeostasis through an accurate sensing of energy intake and energy utilization. Two opposing urges—the need to eat to avoid starvation and the need to stop eating to prevent excess weight accumulation—are primarily regulated by the nervous system and gut peptides: the "gut–brain axis." First described several decades ago, this axis comprises complex pathways enabling gut peptides to acts as both endocrine hormones and paracrine neurotransmitters to affect neurons in the hypothalamic and brain stem centers that regulate appetite.

"Satiation" refers to processes that promote meal termination, thereby limiting meal size. "Satiety" refers to postprandial processes that affect the interval to the next meal and thereby meal frequency.[2] This differentiation is important when considering specific physiologic neural and humoral signals and pathways that regulate eating behavior. In common parlance, and even in the literature, the term "satiety" is often erroneously used to describe processes that affect meal termination.

The role of the stomach

Filling of the stomach with ingested food is widely perceived to be the key trigger of satiation, mediated by stretch receptors in the stomach wall. Animal studies have shown that rats with externally applied cuffs to the pylorus that block the passage of food into the duodenum will terminate eating when given a large meal.[3] This was attributed to gastric distention, because rats with pyloric cuffs fed smaller, more physiological meals did not terminate eating earlier compared to rats without pyloric cuffs. Conversely, when food is drained from the stomach through an open gastric fistula, the animal will not terminate eating as long as the food is allowed to drain externally.[4] Although these observations support gastric filling as a mediator of satiation, they do not implicate the stomach as the primary source of satiation signals. In the animals with externally applied pyloric cuffs,[3] the amount of food required to trigger meal termination far exceeded that eaten in a typical meal. Interestingly, when rats were allowed to eat for 20 minutes with the pylorus open prior to cuff closure (preloading), they ate less after the closure compared to animals that had no preloading. In the animals with open gastric fistulas, all ingested food drained prior to when it could enter the small intestine, eliminating any role the intestine might play in mediating satiation and raising the possibility that this may have contributed to continuous eating. The role of the stomach becomes more obscure when we consider that up to 40% of a meal has emptied into the intestine prior to meal termination.[5] Thus, distention of the stomach and entry of food into the intestine are virtually simultaneous. The chemical constitution or energy content of food has not been found to trigger satiation in the stomach. In cuffed animals, isotonic saline produced volume related reductions of intake equivalent to the same volumes of an energy dense diet. Nutrient concentration, osmotic concentration, and pH also had no differential effect on food intake.[6]

The role of the duodenum

The above-mentioned animal cuff studies provided the first evidence that the duodenum plays a role in meal cessation. Comparing the amounts of food eaten by rats with open and closed cuffs, rats with an open cuff (pylorus) terminated eating more quickly and ate less than rats with a closed cuff.[7] In human volunteers, infusion of lipid solutions into the duodenum reduced the sensation of hunger prior to a meal and slowed the rate of ingestion.[8] This effect did not occur when the same lipid solutions were infused into the bloodstream. The suppression of hunger by the duodenal lipid may explain why eating a bar of chocolate prior to a meal "spoils the appetite." This is typically after a delay of about 15–30 min, which corresponds to entry of the chocolate into the duodenum with gastric emptying. Other physiological experiments have shown that enrichment of a breakfast with fat without any change in the amount of food consumed suppressed feelings of hunger for lunch 4 hours later and reduced food consumption at that meal.[9]

In animal and human models, both real and sham feeding are reduced by intestinal infusions of all three macronutrient groups: carbohydrates, fats, and amino acids. In a clinical study to determine the relative sensitivity of the duodenum to different macronutrients, lipids, glucose, and a control solution (saline) were alternatively infused into the duodenum prior to meals to 20 male volunteers.[10] When infused in equienergetic aliquots, lipids suppressed energy intake by 22% compared with the control infusion and by 15% compared with the glucose infusion. Thus, the duodenum responded not only to the presence and volume of nutrients, but also deferentially to the caloric content of the nutrient. The return of hunger (satiety) has been found to be directly related to a decline in the exposure of the upper small intestine to nutrient stimuli.

Cholecystokinin

Satiatiation signals are triggered as soon as chyme enters the duodenum. These signals are mediated by peptides that are released from enteroendocrine cells in the intestinal wall. The peptides diffuse through the wall of the gut to activate nearby vagal- and spinal afferent fibers from neurons within the ganglia. Peptides also enter the bloodstream to act distantly as hormones.

The peptides therefore act as both neurotransmitters and hormones.

There is a wealth of evidence supporting cholecystokinin (CCK) as the key peptide mediating both satiation and satiety. CCK was described first about four decades ago, although its existence was suggested as early as 1906.[11] CCK is produced and stored in the epithelium of the duodenum (I cells) and released in response to the passage of nutrient byproducts such as lipids and peptides. CCK acts as a neurotransmitter activating vagal afferents, and these vagal afferents in turn trigger or communicate with various centers in the hypothalamus and the hindbrain and the brain stem. It also acts as a hormone and acts directly on the brain. The result is that meal size is reduced (satiation), and the desire to eat between meals is suppressed (satiety).

CCK also acts locally on neurons in the enteric nervous system to regulate motility, digestive enzyme and fluid secretion, and secondary peptide secretion. CCK has a stimulatory or amplifying role on the gall bladder (contraction), the liver (bile acids secretion), and the exocrine pancreas (digestive enzyme secretion). CCK also acts as an incretin to stimulate the beta cells of the pancreas to release insulin. CCK inhibits stomach motility (creating gastric paralysis) while simultaneously stimulating the contraction of the pylorus, thereby preventing food from exiting the stomach into the duodenum. This is consistent with a physiological shift from an ingestive to a digestive phase (Fig. 1).

CCK is the only confirmed physiological satiety peptide. There is a temporal link between nutrient-stimulated CCK secretion and the inhibition of food intake. This has been demonstrated in many studies. The infusion of CCK at physiological doses reduces food intake and stimulates the feeling of fullness in humans.[12] In the sham-fed rat with an open gastric fistula, intravenous CCK reduced intake compared to persistent eating in rats that did not receive CCK.[11] CCK may work in synergy with other anorexic neuropeptides, such as GLP-1 and PYY produced in the distal ileum, and leptin produced by adipose tissue have been found to amplify the action of CCK.[13]

Blocking CCK receptors antagonizes the satiating effects of CCK. In humans, administration of MK-329, a specific peripheral-type CCK receptor antagonist, leads to increased meal size.[14] Otsuka Long–Evans Tokushima Fatty rats that lack CCK1R become obese owing to an increase in meal size and overall hyperphagia, compared to control rats.[15]

The ideal endoscopic treatment

The ideal endoscopic treatment should follow a physiological mechanism of action and preserve normal anatomy. It should allow the patient to eat normally and maintain normal absorption, with the intention of only reducing caloric intake. It should have no adverse side effects and should not burn bridges to other possible therapies. If the treatment is not tolerated or ineffective, the device should be removable. Removability may also be desired if the treatment has achieved its therapeutic goal, in which case repeatability should be an option.

The hallmark of a successful endoscopic device is simplicity of design. Historical examples are the polypectomy snare, sphincterotome, and Dormia basket. The device should be easy to deploy and the procedure should be quick to perform, without requiring any special skills or training.

Duodenal flow restrictor

The author has developed and is testing a duodenal flow restrictor (SatiSphere Duodenal Insert, EndoSphere Inc., Columbus, OH, USA) designed to amplify physiologic satiety signals generated in the duodenum (Fig. 2A). The device has multiple mesh spheres that act as "speed bumps" to reduce the flow of chyme in the duodenum (Fig. 2B). This prolongs the contact time of by-products of nutrition with the lining of the duodenum, which stimulates receptors such as CCK-A on the I cells to release anorectic neuropeptides. The distention of the duodenum by chyme may also stimulate the firing of baroreceptors. The soft spheres distributed along the length of the backbone exert gentle contact with the duodenal wall, stimulating the mechanoreceptors. The signaling from multiple receptors amplifies the satiation effect, "tricking" the brain into believing that adequate amounts of food have been consumed, leading to meal termination. Maintenance of this stimulatory effect may occur by a

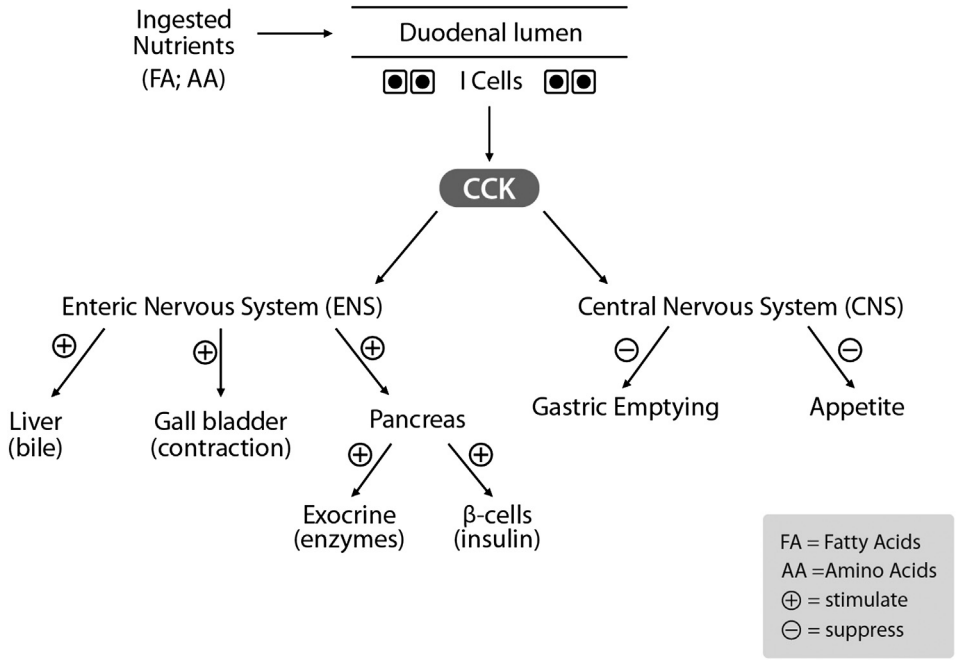

Fig. 1. Physiologic role of CCK on the enteric and central nervous systems (ENS, CNS). CCK, cholecystokinin; CNS, central nervous system; EMS, enteric nervous systems.

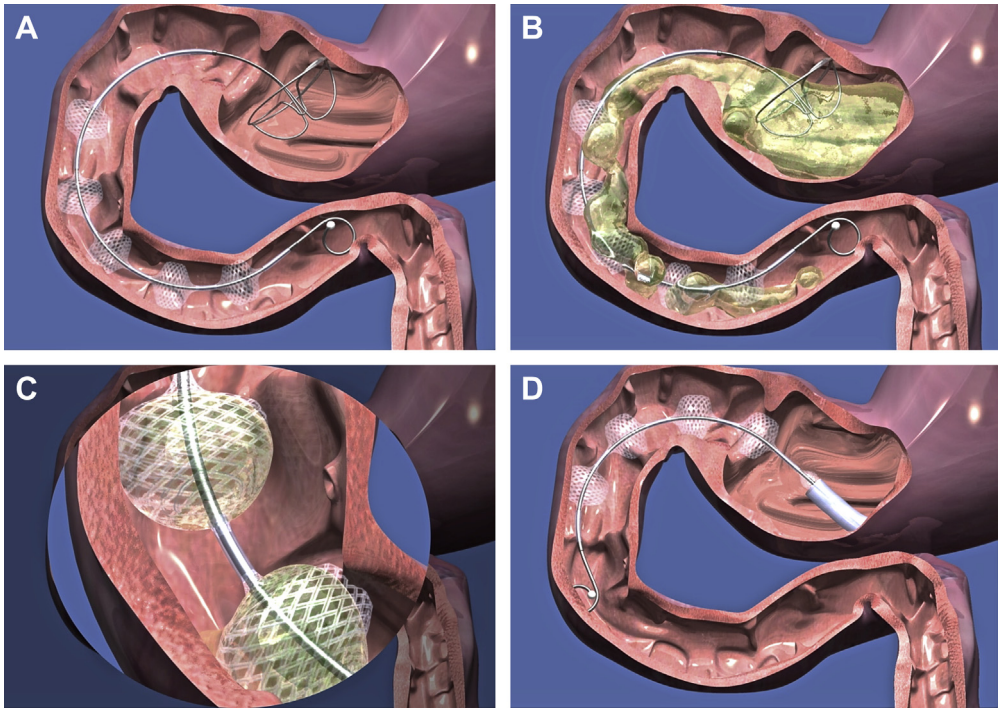

Fig. 2. SatiSphere device. Mesh spheres are distributed along the length of a (A) nitinol backbone, acting as "speed bumps" that (B) delay the passage of chyme. (C) The open mesh retains the ingestate within them for a longer period. (D) Endoscopic removal through an overtube.

number of mechanisms including retention of nutritional by-products in the open mesh spheres and continuous mechanical contact of the device with the duodenal wall (Fig. 2C). Additionally, GLP-1 and fatty acid metabolites such as long-chain fatty acid acyl-CoA may act as incretins, having a beneficial effect on diabetes.

A first-generation SatiSphere device was evaluated in a 2:1 randomized clinical study in 31 patients with a mean body mass index of 41.3 kg/m^2.[16] Twenty-one patients were treated with the device and compared with 10 controls. Weight loss after 3 months was 6.7 kg in patients completing therapy and 2.2 kg in the control group. Excess weight loss was significantly increased by the SatiSphere device (18.4% in completers and 4.4% in controls ($P = 0.02$), resspectively. Dietary restrictions were not imposed. Patients commented that they were no longer able to eat large meals and had lost the desire to eat between meals. Measuring glucose, insulin, and glucagon-like peptide 1 (GLP-1) following a mixed-meal test with the device in place and after removal ($n = 7$), the SatiSphere device delayed glucose absorption and insulin secretion and altered kinetics in GLP-1 levels. The SatiSphere insert was found to be consistently deliverable in less than 15 minutes and removable in less than 10 minutes.

A high rate of device migration (nearly 50%) in patients treated with the first-generation SatiSphere device has led to the development of a second-generation device that adds a proximal anchor in the stomach to prevent distal migration. There are no sutures, clips, or barbs that might damage the tissues. Unpublished pilot data using the second-generation device have shown this configuration to withstand the force of peristalsis that moves contents aborally through the gut.

The SatiSphere device is deployed by first advancing the endoscope to the transverse duodenum. The insert is then pushed through the working channel (the proximal anchor and spheres collapse to allow for passage through the scope). As the insert begins to exit from the scope, the scope is withdrawn at the same rate, in a one-to-one fashion, no different than placement of a stent. The spheres and proximal anchor expand as they exit the scope. The device can be removed endoscopically through a proprietary overtube (Fig. 2D).

Conclusion

The historical treatment of obesity is rooted in the surgical paradigms of forcing the patient to eat less or absorb less. This was founded on the perception of obesity as a problem of willpower, rather than a disease. Today, obesity is widely recognized as a metabolic disease. Our understanding of the mechanisms of the physiological control of hunger and satiety opens the door to new therapies. The duodenum, with its production of anorexic and incretin peptides, has come to occupy a central place in the complex neuroendocrine interactions that underlie the regulation of energy balance. What we need are simple and smart devices that restore physiologic pathways. The mechanical model is giving way to a new physiological model that treats the severe disturbances in energy and nutrient balance.

Conflicts of interest

Dr Binmoeller is the Founder and Chief Medical Officer of EndoSphere, Inc.

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