Pediatric Obesity

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"Obesity represents the most common chronic illness of children and adolescents" (1)

"Until we know how to prevent it, treating obesity is our only choice" (2)

Obesity is a serious life-threatening disease that affects an increasing number of children in the developed world. Obese children suffer in many physical and psychosocial ways and their burden has important consequences to our society. Whereas obesity prevention is the ultimate goal, currently and into the foreseeable future, there will be a significant subset of our children suffering from significant life-altering weight comorbidities. Currently, non-surgical weight loss strategies have met with very limited success but weight management clinics that offer a surgical treatment option have been effective at achieving sustained weight loss and resolution of weight-related comorbidities. A collaborative multidisciplinary approach to the management and care of obese children is essential for success. Choosing a weight loss surgical strategy for children and adolescents should be patient specific and based on their age, severity of comorbidities and their BMI. We have developed a treatment algorithm for the care of obese adolescents as well as a plan for the development of aggressive treatment options for obese preteen aged children based on the limited existing literature and our experience treating adolescents and children at The New Hope Pediatric and Adolescent Weight Management Clinic between 2005 and 2011 at the University of Illinois College of Medicine. (3) As surgeons we must continually test our treatments, evaluate our results, and improve the care we offer our patients.

The Disease of Obesity

Introduction

It is not surprising that modern society is faced with an obesity epidemic. Our energy intake and storage mechanisms are uniquely adapted to our previously primitive diets which included often irregularly spaced low-caloric density foods encased in slow-to-digest cellulose. This diet required the ability to quickly ingest a large quantity of food into the stomach and upper gastrointestinal tract. A long length of small intestine was necessary to allow for digestion and nutrient absorption. Only when the food reached the distal gastrointestinal tract and there was a risk of caloric wasting via dumping and diarrhea, did the brain receive signals to stop consumption. The storage of surplus energy was crucial for survival during famine. Now in modern times, our primitive GI tracts and energy homeostasis mechanisms have not been able to adapt to the improved economic infrastructure that enables and encourages a sedentary lifestyle with very little energy expended on food hunting and gathering; where large quantities of high-caloric-density and easy-to-digest food are readily available; and where enhanced public sanitation and infectious disease control decreases the burden of chronic health problems. The net result is the creeping epidemic of obesity.

Obesity throughout history

Ancient figurines from 20-25,000 years ago depicted obvious obesity and in more recent times, obesity was seen as a sign of affluence and success. In the past two hundred years, obesity has become a negative physical attribute linked to an increasing number of medical and psycho-social problems. Common sense approaches to the treatment of obesity were aimed at limiting food intake and increasing physical activity. Such measures clearly can work for the slightly overweight to minimally obese motivated individual who has the discipline to undergo significant lifestyle change. For the majority of seriously overweight people, diet modification and exercise have minimal success and a high recidivism rate. (4) (5)

In the second half of the 20th century, the increasing prevalence of patients with life altering obesity prompted the development of surgical procedures for the treatment of obesity. Initial bariatric procedures, such as the jejunoileal bypass, were designed with limited understanding of the underlying physiologic mechanisms controlling hunger, satiety, caloric absorption, malnutrition and the bystander effects on the liver and the body as a

whole. (6) In the past quarter century, weight loss surgery has become more refined with combinations of intestinal bypass to interfere with caloric absorption and a variety of restrictive procedures and devices to restrict caloric ingestion. Research has been slow to unravel the puzzle of obesity, and in fact has discovered an increasingly complex array of signals that control energy homeostasis. (7) Significant work remains to be done to understand how these mechanisms increasingly fail when interacting with the social, economic, and environmental changes of our modern society. The long term goal is to prevent and treat obesity with non-surgical means. As we will see, this goal is currently well out of reach.

Definition

Obesity is defined as a long-term positive imbalance between energy intake and expenditure, with increased adipose tissue lipid storage and number of fat cells. (8) The Centers for Disease Control and Prevention (9) recommend using the percentile Body Mass Index-for-age and gender (BMI-for-age) charts to screen children who are overweight or obese. Children with BMI at > 85th percentile are considered overweight and those with BMI at > 95th percentile are considered obese (10). Those with BMI > 99th percentile are considered severely obese.

Incidence

In the past 30 years, the incidence of obesity in children has increased from less than 5 % to approximately 20% in the United States. (10) Interestingly, childhood obesity in most developing countries is a problem of urban children of a higher socioeconomic class. In the United States, the largest increase of obesity in children is seen in the urban poor. (11)

A closer analysis of these trends reveals that between 1976-1980 and 2007-2008, obesity increased from 5 to 10.4% in the 2-5 year age group, from 6.5 to 19.6% in the 6-11 year age group, and from 5 to 18% in adolescents aged 12-19 years of age. (10) (12) Despite these numbers, pediatric research in surgical procedures, surgical devices and drugs has been almost exclusively performed in adolescents and not in the pre-teen years. Preventive dietary counseling, activity recommendations, and behavioral support for younger children have been mostly unsuccessful but may be somewhat responsible for the recent leveling off in the rate of rise of obesity among our youngsters. At the present, 15 to 20% of our children are still faced with the medical, social and economic challenges of obesity. (12)

Etiology

The metabolic constitution of the morbidly obese patient appears to disrupt the normal balance of energy inflow and energy outflow in violation of the basic law of physics and thermodynamics. How can children from the same parents in the same household with similar consumption of calories vastly differ in body compositions? There are aspects of energy homeostasis underlying the body's energy balance set-point accounting for these differences which we do not fully understand in morbidly obese children, and which may be very difficult to modify after a certain stage of post-natal development. The most visible and obvious indicator of this aberrant set-point is increased body fat mass. Intensive research is ongoing to better understand how the metabolically active fat "organ" interacts with and dynamically responds to signals from its environment, the central and peripheral nervous system and other key organ systems in the body. (13)

Calories: Supply and Demand

When combined with increased sedentary activities (accompanied by the opportunity and expectation of snacking outside mealtime), our high caloric-density diet is a major contributor to obesity. Historically, our caloric expenditure was part of the physical activities of daily living such as food and water procurement, manual labor or walking. In modern society, fewer engage in heavy manual labor. Physical activity has instead become something we voluntarily perform to maintain our health and in our leisure time. In addition, rather than eating because of hunger and satiety, we eat out of habit and expectation. Our current diet frequently consists of meals, fluids, and snacks that have a high-caloric density and a high glycemic index (a measure of how rapidly glucose appears in the blood after carbohydrates are ingested).

The biologic controls of caloric intake are hunger and satiety. The physiology of these sensations involves hormones, neural transmitters and their receptors. (13) (14) One such signal is mediated by leptin which is produced by fat tissue and suppresses hunger. Its level is proportional to fat mass. Patients with the rare syndrome of congenital leptin deficiency suffer from severe obesity. With leptin replacement, they stop eating and lose fat mass and weight. Obese patients are not leptin-deficient but are considered to be leptin-insensitive as administration of leptin does not reverse their obesity. (13)

Ghrelin, a hormone produced in the stomach and pancreas, stimulates hunger and enhances visceral fat deposition. Ghrelin is a potent stimulator of growth hormone production. (13) Surgical procedures that bypass a large portion of the stomach (Roux-en-Y gastric bypass [RYGB]) or that excise a large portion of the stomach (sleeve gastrectomy [SG]) are associated with reduced ghrelin levels. Research scientists have developed a vaccine targeting ghrelin that interferes with ghrelin signaling in the central nervous system and that reduces weight gain in rodents and pigs. (13)

PYY and GLP-1 hormones are produced in the ileum and the colon; in response to intraluminal food they suppress hunger. Interestingly, obese people have significantly longer small intestines than non obese people and this may delay the release of these important satiety signals. (13) Procedures that increase the speed of arrival of food in the ileum may suppress hunger.

External factors, such as obesogens (ex. Tributyltin and tetrabromobisphenol A), may affect our caloric utilization. Obesogens, or endocrine disruptors, are functionally defined as chemicals that inappropriately alter lipid homeostasis and fat storage, change metabolic set-points, disrupt energy balance, or modify the regulation of appetite and satiety to promote fat accumulation and obesity. (15) Their increased presence in our environment parallels the rise in obesity in our society. The effects of exposure to these chemicals in childhood and the development of obesity are currently being investigated. (16) (17)

Another potential obesity modulator is gastrointestinal tract flora. (18) The guts of obese mice and obese people harbor an array of microbes (microbiota) which are different from that of their lean counterparts. (19) The gut microbiota and its microbiome (gene content) change with obesity and during weight loss. (20) While intriguing, these observations may simply be associative and require further study to establish the cause or effect relationship and its mechanisms.

Effects of Medications

Medications are a part of our modern environment. Many medications have effects on salt and water retention and on hunger. Others may have effects on calorie utilization. Medications such as glucocorticoids, anti-diabetic drugs, antidepressants, anti-epileptics and antihistamines are known to be associated with weight gain. (21)

(22) Children with a tendency towards obesity may be susceptible to weight gain with the use of these drugs. The interaction of drugs and obesity is an important consideration for all pediatric providers caring for an obese child.

Genetics

Obesity can be thought of as maladaptation of a child's physiology to genetic or epigenetic factors in our modern environment. While the children of obese parents are much more likely to be obese themselves and identical twins raised separately are more likely to be obese if their biological parents were obese (26), the mother and father from the same household with similar diet and opportunities for physical activity can also have both lean and obese children.

In fact, the causes of childhood obesity may be polygenic. (23) Specific genetic mutations are involved in the rare cases of Prader Willi Syndrome and leptin deficiency. Genome-wide association studies revealed that common variants in the first intron of a gene called *FTO* and variants near melanocortin-4 receptor gene (*MC4R*) are strongly associated with obesity and seem to be involved in energy homeostasis signals in the CNS. These genetic findings have identified important pathways in energy homeostasis for certain obese children and may become useful genetic markers to identify at risk children who might benefit from earlier or more aggressive interventions. (24) (25)

Co-Morbidities: Physical and Psychosocial

Obesity is a significant health risk. As the incidence of childhood obesity grows, pediatric clinicians now detect in childhood and adolescence many of the same chronic illnesses and risk factors which are seen in adults. Co-morbidities of pediatric obesity include insulin resistance and type 2 diabetes (27), polycystic ovary syndrome (PCOS) (28), hypertension (29), hypercholesterolemia (30), dyslipidemia and cardiovascular disease (31) (32), sleep apnea (33), asthma (34), nonalcoholic fatty liver disease and nonalcoholic steatohepatitis (NASH) (35), orthopedic disease conditions (36) (37), and pseudotumor cerebri. (38)

Obesity is causing a rapid increase in the incidence of Type II diabetes which historically was a disease of obese, middle-aged patients. Now a significant number of new type II diabetics are children, some presenting in the preteen years. (27) In its early stages, Type II diabetes is a problem of insulin insensitivity that can be treated with weight loss. The prolonged demand on the pancreatic beta cells to produce supra-physiologic amounts of insulin

eventually results in pancreatic insufficiency, at which point, significant weight loss will not reverse the need for exogenous insulin. (39) The course and development of complications of type II diabetes in children has a similar timeline to that seen in adults. It is logical to expect that diabetes-associated comorbidities (cardiac, renal, peripheral vascular, and ocular problems) will prematurely occur in these obese children as they grow into adulthood. (40) (41)

Briefly, common obesity-related medical comorbidities in children (42) include:

1) Sleep apnea has a negative effect on school and work performance and is associated with premature death in young adults who developed obesity as children. 2) NASH is the second most common reason for pediatric liver transplantation. 3) PCOS is a major source of social difficulties for obese teenage girls and is associated with anemia and infertility in obese young women – many of whom became obese as children. 4) Slipped capital femoral epiphysis (SCFE) and Blount's disease are becoming more common in obese children and frequently result in multiple orthopedic interventions with the risks for permanent disabilities. 5) Metabolic syndrome; associated with obesity and defined in adults as a combination of 3 or more of the following: elevated blood pressure, elevated fasting glucose, increased waist circumference, low HDL cholesterol and elevated triglycerides. In children, there is little agreement on the parameters of metabolic syndrome due mostly to the wide range of normal values for these metabolic measurements in childhood and adolescence. These comorbidities are preventable and to some extent, treatable with weight loss.

Obesity also has a major impact on an individual's mental, psychosocial, and economic health. (43) Emotional co-morbidities include low self-esteem, negative body image, and depression. These can be directly related to the child's obesity as demonstrated when their quality of life evaluations improve after successful weight loss. (44) Social co-morbidities include isolation, stigmatization, negative stereotyping, discrimination, teasing, and bullying. (45) Social science analysis clearly demonstrates the prejudice against obese children by their non obese peers, teachers and general society. In obese children, these social comorbidities often result in poor school performance and incorrect diagnosis of learning disabilities. Frequently, these children end up in home schooling situations. (45) Economic co-morbidities take the form of wage penalties, fewer promotions and wrongful termination. (46) As the children become wage earners, their poor school performance, their lack of advanced training, the physical limitations of their size and weight, and their absenteeism from the obesity related clinical comorbidities lead to a reduction in their wage earning potential. (46)

Obesity: A problem for patients, parents, health care systems and society

All children want to be able to fit in with their peer group and to do the things the other children do. Quality of life questionnaires and personal interviews with obese adolescents consistently demonstrate a sense of desperation from their inability to "keep up" with their peers in all physical and social activities. (44) Obese adolescents often present to the weight management clinic with a sense of resignation and helplessness brought on by years of emotional scarring and failed attempts at weight loss.

The obese child's parents in turn experience significant blame and guilt for their children's obesity. These parents are often told by others, not the least, by health care professionals, that they are the cause of their child's problem for having the wrong genes, for their parenting style, and for their personal ignorance, laziness, thoughtlessness, lack of love, or selfishness. (47)

Hospitals and the healthcare system have a responsibility to treat the disease of obesity in children. They need to be aware of obesity-specific issues of the obese child presenting with standard medical problems (48) including the need for specialized furniture and equipment such as sphygmomanometers and commodes, different transfer techniques, the variability in how their body composition and physiology change the pharmacodynamics of different drugs, and the direct correlation of obesity with increased length of hospitalization and complication rates. (49) Furthermore, hospitals and healthcare personnel need specific training to overcome their bias and lack of knowledge about obesity and obese children. In order to address these issues, obesity should be a diagnostic item in the patient's problem list to identify them at the time of admission as a special patient population and alert the personnel and healthcare providers to their particular needs.

From the point of view of an economist, the long term societal effect of childhood obesity is sobering. Health care costs associated with obesity-related illnesses for children and adults are estimated at $147 billion per year. (51) The costs of caring for obese children with typical pediatric diseases such as asthma and appendicitis are increased by their longer hospitalizations and their higher incidence of complications. (52) Obesity comorbidities are chronic, progressive, and pediatric obesity healthcare costs are likely to be carried over into adulthood. On an individual basis, some progress is seen on payers' reimbursement of obesity related services, but for the most part, coverage of recommended treatments for pediatric obesity through Medicaid or private insurance is ensured in only

a very few states (53) (54). Furthermore, it has been well established that obese people have fewer educational opportunities and therefore fewer and lower paying job opportunities. (46) Their economic productivity is also compromised because of the work time lost from the high rate of associated comorbidities and disabilities. (55) It is important to note that national security may be adversely affected as greater than 20% of young men and 40% of young women do not qualify for the United States armed forces because of their obesity. (50) The gloomy economic outlook for obese children growing into adulthood boils down to less economic productivity and more cost to society.

Obesity Treatment

Why treat obesity?

Society demands that healthcare providers aggressively treat children suffering from an illness which has serious clinical life threatening consequences. Therefore, it is puzzling why leaders in pediatric healthcare, government and third party payers have been loath to embrace aggressive treatment for morbid obesity in children. This reluctance is in denial of the fact that the child suffers from serious clinical, psychological, and social comorbidities directly related to obesity and that the best treatment for any of these comorbidities is for the child to achieve a healthy weight. Reluctance to effectively treat childhood obesity ignores the serious economic burden of the comorbidities of obese children which will be carried into adulthood. While there might be opinions that children do not need treatment for obesity because they will grow out of it, the data clearly demonstrate that adult obesity usually starts in childhood and is correlated with the duration and degree of childhood obesity. (56, 57) Aggressive management strategies for children are therefore needed.

For obesity and bariatric interventions, many treatment recommendations are currently restricted to adolescents – ages 14 through 18. The inclusion of bariatric procedures in weight management protocols for children should be *need* related, not *age* related. (58) The surgical and device options must be carefully considered and developed to minimize risks and anatomical rearrangements and maximize control of the comorbidities associated with obesity. The risks need to be balanced against the larger benefits of weight reduction on comorbidities. From a philosophical standpoint, the idea of exposing a child to a bariatric surgical procedure has traditionally met with significant opposition from pediatric primary care physicians and society at large. This philosophical resistance is inconsistent with our current management approaches for other pediatric diseases.

Historically, sick children receive treatment when they have a problem, regardless of their age. A problem is first recognized and the best treatment for their problem is devised. Treatment regimens are frequently multidisciplinary and frequently involve risks (e.g. radiotherapy and chemotherapy for cancer, immunotherapy for inflammatory bowel disease, surgical reconstruction for GI tract anomalies, and cardiac surgery for cardiac anomalies) which were accepted because the benefits of treatment outweighed the disease. Similarly, obesity shares many of the life threatening aspects of cancer or coronary artery disease albeit on a longer time scale since obesity currently remains a chronic and incurable disease. 59 The same issues of obesity treatment pertaining to how to work with children in different developmental stages, how to facilitate treatment compliance, how to deal with families of different capabilities, and how to provide chronic, multidisciplinary care are questions pediatric healthcare providers have already addressed for many other diseases.

Prevention measures may one day lead to a significant decrease in obesity. A more complete understanding of the multiple factors involved in obesity and how they interact with each other will someday lead to effective and individualized non-surgical treatment protocols, or new pharmacologic agents that curb appetite, decrease calorie absorption or increase metabolic rates without significant side effects. Additionally, endoscopic techniques will be developed that allow for the deployment of devices that interfere with absorption or appetite without significant surgical risk. In the meantime, without bariatric treatment, an entire generation of obese youngsters is at risk of prolonged morbidity and early death without some form of effective intervention.

Core Treatment Program for Weight Management

There are three essential core elements to any adult, adolescent or pediatric weight management program: nutrition education, activity guidance, and behavioral modification/support. Ideally, the pediatric/adolescent multidisciplinary weight management team should include pediatric specialists in the following disciplines: medicine, surgery, nursing, nutrition, activity, and mental health. Pediatric subspecialists need to be available to manage obesity related comorbidities.

Nutritional guidance and training is a basic tool of weight management. With an increasing number of families not eating at home and not preparing their own food, families come under the influence of advertising and convenience rather than healthy nutrition. Certainly larger portions, additives in foods to improve shelf life, and

sweeteners in liquids are correlated with the increase in obesity statistics, but direct physiological pathways remain to be worked out. Education and training in portion size, reading labels for additives, and noting calories in liquids are basic education to improve everyone's nutritional health. (60) The dietician considers economic and cultural issues when developing educational materials.

Activity prescription is designed to achieve basic cardio-respiratory fitness; matching activity to the physical capabilities of each person. Obese people cannot successfully participate in activities designed for lean people. They need unique equipment, unique intensity goals, and unique duration goals. In a sense, they are physically handicapped and can be best served by physical therapists. Raising awareness about the economic, cultural, geographic, and seasonal obesity potentiating aspects of our modern society such as where to park the car, who walks the dog, the safety of the neighborhood, the availability of indoor facilities in inclement weather, and how long to walk at the mall before shopping can be part of the activity education. 61

Ongoing psychological/behavioral support remains the third basic component of weight management in obese children. Using the same quality of life assessment tool, it has been shown that obese children's rating of their quality of life was lower than that of a group of children with cancer. (62) No child wants to be obese; almost all have failed previous attempts at achieving a healthy weight. Childhood obesity is associated with emotional and behavioral problems from as young as age three years with boys being especially at risk. (63) While obese children and their families respond when utilizing the tools of nutrition, activity, and behavioral support, (64) the 10% loss of excess body weight (65) and the high rate of recidivism are disappointing and speak to the need for further research and efforts into the treatment of obese children

Adjunct Therapies to the Core Treatment Program

Pharmacological treatment

There is no pharmacological cure for obesity. In general, drug investigations have been conducted as a single treatment but should only be considered within the context of a long term, multidisciplinary weight management program. Specific drugs used in obesity therapy are discussed in this section.

Orlistat (Xenical) is approved for use in obese children 12 years of age and older. Orlistat inhibits pancreatic lipase production to reduce fat absorption. Its long term applicability for a chronic disease like obesity is

limited by the major side effects of liquid, fatty stools and abdominal pain. Orlistat may be useful during the initiation phase of a multidisciplinary weight management program or for intermittent use to help maintain weight loss/control. (5)

Other drugs are related to amphetamines and suppress appetite. Sibutramine (Meridia) was recently removed from the market because of the risk of myocardial infarction and stroke. Rimonabant is a cannabinoid (CB1) receptor antagonist which failed to gain FDA approval because of its psychiatric side effects. (5)

Hormone analogs such a GLP-1 analog and an Amylin analog suppress appetite and are being studied as antiobesity drugs. (66) GLP-1 is produced in the ileum and colon in the presence of food while Amylin is produced in the pancreas in response to the presence of food in the proximal small bowel. Lorcaserin (a serotonergic receptor agonist- appetite suppressant) and the combination drugs Qnexa (appetite suppressant/stimulant and anticonvulsive) and Contrave (antidepressant and anti-addiction) are currently being studied. (66)

Bariatric Surgical Procedures in Adolescents

As previously mentioned, the non-surgical options for weight loss in morbidly obese adolescents have limited effectiveness. Surgical interventions for obesity were initially developed for morbidly obese adults and later applied to adolescents. (67) In response to concerns for the unique aspects of adolescent children, a number of pediatric surgeons rose to the challenge of adolescent bariatric surgery by beginning in-depth studies of the various surgical options and developing adolescent weight management programs. (68) (69) (70) (71) (72) (73) (74) Overall, there is no one perfect bariatric procedure for all obese adolescents. The ability to test these procedures in cooperative multi-institutional prospective trials should allow this field to advance rapidly. Historically, weight loss procedures were developed to minimize caloric intake (restrictive procedures), control caloric digestion (malabsorptive procedures) or to combine both effects. Table 1 offers a detailed comparison of the more commonly performed procedures including the Laparoscopic Adjustable Gastric Band (LAGB), the Sleeve Gastrectomy (SG) and the Roux-en-Y Gastric Bypass (RYGB).

Surgical Approaches to Weight Loss in Adolescents

The ideal bariatric procedure would result in durable and substantial weight loss, with minimal risk from short term procedural complications and long term malnutrition, growth limitation, liver problems, malignancy or

mechanical complications. These issues are crucial in the process of choosing a suitable weight loss procedure for adolescents. However, significant disagreement on the best bariatric surgical procedure for adults, much less for children, remains. Each of the procedures has its own advantages and disadvantages (See Table 1). There is no randomized clinical trial comparing the effectiveness among bariatric procedures in adolescents. Definitive comparative studies are rare and sometimes yielded contradictory results. (75) (76) It is however encouraging that individual adolescent weight management programs are increasingly reporting on their own adolescent experience. (77) (78) (79) (80) (81) (82) (83) (84) (85) Overall, very good weight loss response and rapid improvements in all comorbidities, including enhanced physical and psychosocial quality of life along with low morbidity, have been reported.

Factors in evaluating weight loss procedures in adolescents

As previously mentioned, the current literature does not provide easy answers to the ideal operation for morbidly obese adolescents. There are no available parallel comparisons of the RYGB and LAGB in teens; limited data are now available describing the use of the SG in adolescents. Current clinical guidelines for adolescent weight loss surgical procedures are primarily based on the pros and cons analyses of the various procedures for both adults and adolescents. (86) (87) (88) (89) (90). To address this lack of definitive data, the Longitudinal Assessment of Bariatric Surgery (LABS) consortium were established and supported by the NIH in 2003 to promote collaborations between surgeons working with obesity. The adolescent version of this consortium, Teen-LABS, was started in 2007 to collect available data with the hope to develop guidelines for the optimal adolescent weight loss management strategy. (71)

At this juncture, our recommendations are based on our evaluation of the more extensive adult data combined with the limited adolescent series and our own experience. We now provide a brief review of the existing bariatric procedures in use in children to help frame the discussion and offer standardized treatment protocols.

The LAGB is an effective procedure for 60-80% of patients and is especially effective for patients with a BMI of 50 or less with an expected loss of 50-60% of their excess weight over a two to three year period. (91) The LAGB procedure has a short learning curve. The majority of the complications, with incidence as high as 15%, is related to mechanical issues such as the band's position, pouch enlargement, or mechanical port and catheter

problems. In our personal experience, these problems were primarily experienced by patients with poor weight loss who aggregate into a higher BMI (>50) group (Holterman, AX, et al, Journal Pediatric Surgery, manuscript submitted). We have elected to subsequently offer SG in most of these patients or have referred them for RYGB to adult bariatric surgeons.

In comparison, the RYGB is a very effective procedure providing excellent rapid weight loss in most adolescent patients but with a slightly higher mortality rate. (92) The positive weight loss response needs to be balanced against the more serious short and long term surgical complications, including that of micronutrient and vitamin deficiencies from the aggressive anatomical rearrangement. Short and longer term safety concerns associated with the RYGB may limit the referral of morbidly obese patients to centers that only offer this procedure.

The SG is a technically simple procedure that has become a stand-alone, first line weight loss procedure for many adult surgeons. Post SG, patients have minimal risk of micronutrient and vitamin deficiencies and complications are infrequent and manageable. In support of the encouraging mid-term data from adult patients, the American Society for Metabolic and Bariatric Surgery (ASMBS) "*has accepted the SG as an approved bariatric surgical procedure primarily because of it potential value as a first-stage operation for high risk patients, with the full realization that successful long-term weight reduction in an individual patient after SG would obviate the need for a second-stage procedure*". (93) The SG has also been successfully performed as a salvage operation for adolescent patients who do not respond sufficiently to or have mechanical issues with the LAGB (Dr. Robert Kanard, personal communication 2011). Short-term data of the SG as an initial operation in adolescents is encouraging. (94) Concerns for the use of SG in adolescent patients center on decreased ghrelin production and on its adverse effects on growth hormone production and growth. (95) This may be less relevant as adolescents should respond to supplemental growth hormone injections and since most adolescents treated for weight loss surgery have already achieved growth plate fusion.

The Biliopancreatic diversion/duodenal switch (BPD/DS) is a very effective weight loss procedure which is technically challenging with significant short term risks and long term nutritional concerns. (96) This procedure is best understood as a combination of a sleeve gastrectomy and a bypass procedure in which the food that enters the duodenal bulb from the tubularized stomach is diverted into a roux limb (the new duodenum). This limb of intestine

carrying the ingested food mixes with digestive enzymes carried by the native duodenum and jejunum at a downstream enteroenterostomy and thereby limits the available time for digestion and nutrient absorption. The profound anatomical rearrangements and risk of long term nutrient absorption problems associated with BPD/DS is unsettling to most physicians caring for adolescents and therefore precludes its use as a first line bariatric procedure in this age group. The role of the BPD/DS may be as a salvage procedure after insufficient weight loss with the RYGB or SG.

Devices and new procedures

In addition to the previously described bariatric procedures, a number of new devices and one new procedure are under development. Currently, the adjustable gastric band is the only weight loss device in general use. Other devices under consideration have been designed to interfere with normal gastrointestinal physiology in a reversible and adjustable fashion and may be attractive alternatives but require extensive clinical testing before they will be available for use in children.

In this section, we will first discuss the process of FDA approval for device use in the US and give a brief overview of the new weight loss devices under development including various intragastric balloons, the vagal stimulator, the gastric stimulator, and the Endosleeve (duodenojejunal bypass device), as well as new minimally invasive procedures including gastric imbrications, and a procedure that combines the gastric sleeve, omentectomy, and a mid small bowel resection.

The FDA and Bariatric Devices

Devices for the treatment of obesity in children may be an ideal alternative to weight loss surgery since they are seen as a less invasive treatment, may have lower morbidity, and are adjustable, reversible and removable. These factors may make weight loss devices more acceptable as a part of a multidisciplinary weight management strategy in children. It is important to appreciate that the Food and Drug Administration (FDA) has jurisdiction over the use of medical devices (but not surgical procedures) in the United States. Medical devices for use in obesity, therefore, require extensive testing in FDA monitored trials. These FDA approved trials have been performed almost exclusively in adult patients.

The FDA approved clinical indication of a device or medication frequently excludes or ignores the product's use in children citing the lack of data or inadequate theoretical grounds. Therefore, by necessity, many pediatric health care professionals frequently resort to the use of devices and drugs that will never undergo the required clinical testing to attain "FDA approved use in children" status, thus exposing themselves to a potentially vulnerable medico-legal position. Indeed, the pediatric providers have traditionally used clinical judgment in their decision-making to use "off label" medications and devices/equipment and frequently make necessary modifications. Unfortunately, many third party payers will not reimburse for "off-label" usage of a device and hospital risk management often prevent practitioners from the use of "off-label" items. Furthermore, device manufacturers frequently make a business-based decision to avoid the expense of clinical trials in children for a market that is small and more prone to liability. These factors deter the development of weight loss devices for pre-adults and limit the available treatment options to surgical procedures that are outside the jurisdiction of the FDA. It can be argued that this lack of attention to device development and evaluation is a form of discrimination against children.

Temporary Procedures

The intragastric balloon (IB) and the Endosleeve are intraluminal devices which can be considered to be temporary as they are removed or changed on a regular basis. These procedures would be attractive in children whose bodies would revert to a more normal physiology when they achieve a healthy body fat mass. These devices could help the child attain a healthy percentage body fat at which time their use might be able to be discontinued.

Intragastric balloon

The intragastric balloon is designed to be inflated in the stomach and causes a continual sensation of gastric fullness and satiety. Early versions of this concept were not tolerated well because they were not adjustable and caused significant discomfort and vomiting when inflated; they also slowly deflated over time and moved into the lower GI tract, sometimes causing obstruction. Newer versions are expected to address some of these problems. (97) (98)

Current intragastric balloons under development include two non-adjustable free floating balloons filled either with saline (BIB [Allergan Corp, Irvine, CA]) (98) or with air (Heliosphere), (99) and two adjustable systems

(Endogast (100) and Spatz (101)). The Endogast is fixed in position in the proximal stomach via a transgastric catheter system which connects to a subcutaneous port and is adjusted with air insertion or removal. The Spatz is a free floating system with a tube attached that is retrieved endoscopically for adjustments with saline. This adjustability may allow the patient to adapt without vomiting and to better tolerate the presence of the device. Adjustability will also allow the balloon size to be titrated to the size of the patient and to the desired effect. The intragastric balloon systems have been used in adults and a small number of children outside the United States. Based on reports from this limited clinical experience, these devices appear to be safe and effective for temporary use. (102) (103)

Endosleeve

The EndoBarrier™ Gastrointestinal Liner involves a sleeve of impermeable material placed inside the intestine from the proximal duodenum distally into the jejunum. Current versions extend distally for about 60cm. The sleeve is placed and removed endoscopically. The gastrointestinal liner creates a mechanical bypass situation, (as opposed to surgical), by having the food go through the inner lumen of the sleeve where it is excluded from the digestive juices outside the sleeve. (104) This separation interferes with absorption and the usual neuro-hormonal cascade of the bypassed intestine (CCK and Amylin) is not stimulated by contact with chyme. The mixing of food and digestive enzymes at a point further down the GI tract limits time for calorie absorption and prematurely initiates the satiety- inducing neuro-hormonal feedback loop when PYY and GLP-1 are released from the distal ileum. The length of sleeve necessary for an effective device has been determined in adults, but a pediatric version would need to vary in diameter and length based on age. Current design and early studies on adults anticipate that the individual gastrointestinal liners will have a lifespan of about 6 months, at which time, they require endoscopic retrieval and possible deployment of a new EndoBarrier™. An FDA-monitored trial of the Endobarrier™ (GI Dyamics, Lexington, MA) is ongoing in adults in the United States, South America and Europe. It is currently not FDA-approved for use in the United States.

Semi-Permanent Procedures

The vagal blocking devices, the gastric stimulating devices, and the endoscopic gastroplasty techniques are designed for long term usage without permanent anatomical change but can be removed or reversed.

Vagal Blocking Devices

The vagal blocking devices are based on the observation of the lack of appetite and weight loss frequently seen in post vagotomy patients. Subsequent analysis has identified the existence of vagal afferent pathways to the central nervous system that control appetite. This knowledge prompted the development of electronic vagal blocking devices that place leads around the vagus nerves in the abdomen or in the thorax with minimally invasive techniques. These leads are then connected to a subcutaneous power source/control device similar to a cardiac pacemaker or a phrenic-nerve-stimulating diaphragmatic pacing device. Of note, stimulation of the cervical portion of the vagus nerve has been used for years to control seizure activity. These devices seem to be well tolerated long term. The frequency, amplitude, and wave form of the stimulation can then be customized to gain maximal effect on satiety in a given individual. The current subcutaneous boxes are bulky but will decrease in size and become easier for children to tolerate. Early studies of the Maestro System (EnteroMedics™ Inc., St. Paul, MN) in adults show modest weight loss. (105) Trials are now underway in the U.S.

Gastric Stimulators

The use of gastric stimulation to induce weight loss is based on a number of possible mechanisms. The stimulation may interfere with ghrelin production or simulate the sensation of a full stomach, sending afferents messages via the vagus nerve. Trials in adults to date have been disappointing but an effect was realized in some patients. (106) Patient selection and/or a comprehensive weight management approach may improve its effectiveness in children. One gastric stimulation system (Tantalus, MedaCure, Orangeburg, NY), has been used in Europe and is undergoing FDA trial in the United States in patients over 17 years old. (107)

New procedures

Gastric Imbrication

Gastric imbrication involves plicating the greater curve, fundus and body of the stomach to leave a tube along the lesser curvature from the gastroesophageal junction to the pylorus. It mimics the SG without excision of the stomach. The mechanism is presumed to be restrictive with reduction of ghrelin production. In this procedure, gastric ghrelin production is not stimulated because the food stream is excluded from the stomach. The procedure can be performed open, laparoscopically or endoluminally. The endoluminal approach is restricted by the size of the

endoscopes necessary to do the suturing. This may be a limiting factor in children. Whether the lack of stimulation on ghrelin changes the effect on growth hormone in children remains to be determined. The safety of this procedure probably lies somewhere between the devices and the other surgical procedures, and its effectiveness and durability need to be studied. Similarly to the SG, the gastric imbrication procedure should have minimal effect on micro-nutrient absorption. (108) (109)

Combined Gastric Sleeve Resection and Mid Small Bowel Resection

This procedure combines a gastric sleeve resection and omentectomy with a mid small bowel resection. The mechanism is five-fold: 1) mechanical restriction; 2) reduced stimulation of appetite (lower ghrelin levels); 3) increased suppression of appetite (higher GLP-1 and PYY levels); 4) diminished surface area for caloric absorption; and 5) the inflammatory cytokines released from the omental fat are removed helping to spare the liver. (110) Theoretically, malabsorption is avoided by leaving the proximal small bowel intact and in line with the remaining GI tract to maintain fat-soluble vitamin absorption and the enterohepatic circulation of bile salts in the terminal ileum. Small series of this procedure in adults and adolescents have been reported with encouraging results but a longer follow up will be required. (110) (111) It is also not clear as to the optimal resection amount of the mid small intestine. The sequential addition of a mid small bowel resection to a patient who did not lose adequate weight after a SG or RYGB may be a logical and safer next step than the BPD/DS.

Suggested Clinical Management Protocol for Weight Loss in Adolescents and Children

It is becoming increasingly clear to the medical community, and the society at large, that better treatment strategies need to be developed for the care of morbidly obese children. Non-operative treatments have mostly failed or have met with minimal and temporary success. Primary care physicians are frustrated with the current ineffectiveness of non-medical weight loss for morbid obesity but remain unwilling to condone “aggressive” bariatric surgical procedures. In the absence of clear-cut Class I evidence for the relative effectiveness of the various bariatric surgical protocols, it is challenging to set exact guidelines for the management of morbid obesity in adolescents and children. Because of the complex etiologies and variable extent of morbid obesity, a rational approach customizes protocols to the patient’s individual needs by taking into account their age, BMI, type and severity of comorbidities and psychosocial factors. These treatment protocols would provide the structure for

clinical trials to evaluate and refine treatment strategies. We recommend multi-institutional cooperative treatment protocols with critical long-term safety and efficacy analysis, in the same manner the Children's Oncology Group has approached childhood cancer.

It seems most prudent to offer a common sense practical and step wise intensification of the management options. Resolution of the medical and psychosocial comorbidities must be the primary and overarching goal, secondary to the achievement of normal or near-normal weight. Choosing a bariatric procedure based on the morbidity (frequency and severity) and the risk of mortality prioritizes these goals.

Adolescents: Suggested Clinical Management Protocol for Weight Loss (Figure 1)

Group I: Patients 13-19 years old with BMI less than or equal to 50.

Because of their simplicity and low morbidity, the LAGB or SG can be a good first choice for these patients. Morbidly obese adolescents with a lower BMI respond well to the gentle progressive pattern of LAGB weight loss.

Group II: Patients 13-15 years old with BMI greater than 50

From our own experience, adolescents with BMI greater than 50 experienced difficulties with LAGB. They lose the same net weight as their lower BMI adolescent counterparts (A. Holterman, Journal Pediatric Surgery, manuscript submitted), but the large amount of excess weight that remains and the slower pace of the LAGB leads to frustration and unmet expectations. Further tightening of the band to help accelerate weight loss often results in pouch enlargement, necessitating subsequent loosening of the band at the risk of regaining weight. We therefore recommend a more "aggressive" initial procedure such as the SG which would provide additional appetite suppression without the risk of micronutrient deficiencies along with an earlier and faster weight loss response.

Group III: Patients 16-19 years old with BMI greater than 50

In addition to the same factors that limit the effectiveness of LAGB in Group II, the age related maturational independence of this group often leads to less than ideal adherence to treatment. In addition, insurance coverage changes for these adolescents can create a financial barrier to their ongoing care. We

therefore recommend a more "aggressive" initial procedure such as the SG or RYGB which would provide an earlier and faster weight loss response. The shallow learning curve for laparoscopic SG compared to the more technically challenging RYGB and its lower risk of micronutrient deficiencies, may make the SG particularly attractive for this mobile population.

For the subset of patients who require salvage operations for a recalcitrant response to the LAGB, the SG and RYGB may be appropriate. A failed SG is probably best salvaged by a RYGB or BPD/DS procedure or with the addition of a mid-small bowel resection. It is our hope that these patient selection criteria will enhance the success rate of the LAGB and reduce the patient and parent's frustration from unmet expectations and wasted multiple operations.

Children: Guidelines for Developing Weight Loss Strategies

Although obesity can start in infancy and its comorbidities can occur in the very young, treatment outside behavior modification, activity programs, and diet training for obese children less than 13 years old is nearly nonexistent. One needs to be cognizant of many age-specific physiological and psychological issues in the treatment of these obese children. For instance, obese children younger than 13 years old frequently have not completed their linear growth. Their BMI can improve when their weight gain is arrested while their linear growth remains. It is not clear whether this process reduces the body fat mass and resolves obesity related comorbidities. As obese children advance through the developmental stages of infancy, toddler, school-age, preteens, and early teenager years before reaching 13 years of age, the dynamics of food consumption, food choices, and activity decisions are much different from that of the adolescent. Their behavior may be more malleable, and parents or healthcare providers may have a better chance at influencing their compliance. Any treatment program should have a multidisciplinary approach which recognizes the previously described basic tools of weight management – especially when surgical procedures and pharmacological use are part of the therapy. Large study groups with shared protocols and database are strongly recommended.

Of note, it has been our experience that under physician and parents' guidance, younger adolescents are more accepting of the LAGB life-style modifications. Because of the excellent safety profile, reversibility and adjustability of the LAGB which allow controlled caloric ingestion and nutrition without malabsorption, the use of

LAGB may be appropriate to the treatment of younger patients in their pre-pubertal and early puberty years (10-13 years old with advanced obesity with or without comorbidities). Control of food ingestion in this group may allow them to undergo the longitudinal growth that leads to a normalization of their BMI without malnutrition. The adjustable gastric band can then be unfilled and if weight remains within an acceptable range, it could be easily removed.

The FDA can play a larger role in the development of drugs and devices for obesity treatment in children by supporting parallel studies in children, adolescents and adults, taking into account their physical, physiological, and psychological differences as well as their differential responses. The traditional approach to wait for completion of adult trials before proceeding with studies in children neglects the fact that 20-30% of children less than 13 years old affected by obesity are still waiting for treatment. A new paradigm of cooperation is needed between industry, the FDA, the CDC, the NIH, and professional healthcare associations (AAP, NACHRI, AAFP, APSA, ASMBS, etc) to assist pediatric healthcare providers with tools and techniques to care for obese children. Rather than placing the blame on the parents for the lack of effective therapy and taking these children away from their families, the healthcare system needs to come to terms with the challenge of developing effective treatment schemes while keeping these children home with their families.

Summary

Childhood obesity is a tremendous burden for the individual children, their families and for our society. Obesity prevention remains the ultimate goal but rapid development and deployment of effective non-surgical treatment options is not currently achievable given the complexity of this disease. In the meantime, hundreds of thousands of our world's youth are facing discrimination, a poor quality of life, and a shortened life-span from the burdens of this illness. Surgical options for adolescent obesity have been proven to be safe and effective and should be offered. The development of stratified protocols of increasing intensity (i.e. "surgical aggressiveness") should be individualized for each patient based on their disease severity and risk factors. These protocols should be offered in the context of multi-disciplinary, cooperative clinical trials to critically evaluate and develop optimal treatment strategies for morbid obesity. Long-term cooperation between families, schools, communities, government, healthcare professionals, media, insurers, and industry is essential in addressing both the prevention and treatment of childhood obesity.

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