Current Problems in Surgery 59 (2022) 101059

Contents lists available at ScienceDirect

Current Problems in Surgery

journal homepage: www.elsevier.com/locate/cpsurg

Metabolic surgery

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Introduction

-Scott A. Shikora, MD

Humans have been performing surgery since the dawn of mankind. For most of that time, surgery was very straightforward and easy to understand. Surgery was narrowly focused to directly treat an anatomic or physiologic abnormality. The offending tissue or organ was identified and targeted. The surgery was then directed only to the diseased tissues. Generally speaking, surgery consisted of extirpation of the lesion or repair of the injury. For example, symptomatic cholelithiasis is usually treated by a cholecystectomy which is almost always curative. In a similar fashion, a severely painful, arthritic hip is typically excised and substituted with an artificial joint, with good results.

However, over the course of history, some surgical procedures were developed to treat disease by manipulating tissue or an organ not directly the responsible for the patient's disease. For instance, removing the spleen to treat patients with idiopathic thrombocytopenia purpura (ITP) or excising the ovaries in women with breast cancer. In these examples, the spleen was responsible for the ITP no more than the ovaries caused breast cancer.

The use of surgery in this fashion was first described by Buchwald and Varco in 1978 and given the name "metabolic surgery.[1]" They defined metabolic surgery (MS) as "the operative manipulation of a normal organ system to achieve a biological result for a potential health gain.

Presently, the most recognized and effective use of this type of surgery is what was formally called obesity, weight loss, or bariatric surgery (BS). These procedures involved various manipulations of the stomach and/or the small intestine. The original goal was to achieve sig-

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https://doi.org/10.1016/j.cpsurg.2021.101059

nificant weight loss. Over time, it became obvious that the weight loss operations had profound beneficial effects on a number of seemingly independent diseases such as hypertension, type 2 diabetes (T2DM), and liver disease.

Currently, metabolic surgery has been widely accepted by the bariatric community and now it is common to see the terms joined as metabolic/bariatric surgery (MBS). The full potential of MBS is not yet known and it is not yet determined whether these procedures might be of value to non-obese patients with health issues such as diabetes.

In this monograph, we provide a historical view of MS as well as a review of the current literature evaluating the safety, efficacy, and likely future of MBS.

The definition of metabolic surgery

-Henry Buchwald, MD, PhD

In a book entitled, *Metabolic Surgery*,[1] we defined MS "as the operative manipulation of a normal organ or organ system to achieve a biological result for a potential health gain." This definition continues to be valid with the possible addition of "putative" before "normal organ or organ system" to account for the growing evidence that the organs manipulated may have a role in initiating and maintaining a pathologic state (eg, the intestine in obesity and T2DM).

The term metabolic is derived from the Greek and defined as the processes by which a body produces substances and energy to sustain life. The term surgery is derived from 2 Greek words: *cherios*, a hand, and *ergon*, work. Thus, surgeons are hand laborers. Combining metabolic and surgery implies that the discipline of MS is cognitive as well as manual and involves obtaining knowledge and understanding through thought and experience.

For the ancient Greeks, the concept of disease consisted of an imbalance of the 4 humors of yellow bile, black bile, phlegm, and blood. In the 18th to 19th century, the holistic concept of disease was superseded by the "modern" classification of diseases as organ specific. Thus, the heart was responsible for a heart attack, and the stomach and duodenum for benign ulcers. The great Bohemian (Austrian) surgeon and anatomist Rokitansky was the primary advocate for this interpretation. By the late 20th century, however, a holistic perspective started to return to the field of medicine. Science and medicine began to consider disease as a body process gone wrong due to a genetic pre-inclination, a neurohormonal imbalance, and the internal environment (eg, the gut biomere), as well as the influence of external factors (eg, smoking).

The prior principles of surgery—incisional, extirpative, and reparative—were all focused on the organ gone bad, an organ inflicted with infection, cancer, trauma, or malfunction. The principle of MS is not focused on diseased organs but on putatively normal organs with the intent of altering an abnormality in the working milieu of the body.[2] From this perspective, the conviction has emerged that MS, with its induced variegated metabolic processes, has the ability to favorably alter certain of the imbalances of human afflictions.

The history of metabolic surgery: a dissertation on past metabolic procedures

-Henry Buchwald, MD, PhD

Possibly the earliest example of metabolic surgery occurred more than 120 years ago when reduction of breast cancer metastases was achieved by the extirpation of normal ovaries. In addition to endocrine ablations for malignancies, other metabolic procedures became popular in the last century (eg, splenectomy to cure ITP, portal diversion to ameliorate glycogen storage disease, and pancreas transplantation to mitigate type 1 diabetes). Probably the most commonly performed metabolic surgical procedure prior to the introduction of bariatric surgery was surgery for peptic ulcer disease. This surgery involved the resection of various segments of normal stomach and the division of branches of normal vagus nerves in order to cure a distal duodenal ulcer that remained, except for emergencies, untouched by the hand of the surgeon.

Introduced in 1962, with the first human procedure performed on May 23, 1963, the partial ileal bypass operation for hyperlipidemia is an example of MS by intent, as well as by outcomes.[1,2] The most cited example of MS today is BS, which with a shotgun blast of metabolic alterations favorably affects a multitude of causal obesity mechanisms.[1,2] Many other current applications of MS are discussed in the following sections. Still more are being explored, (eg, treatment of resistant depression by electrostimulation of the subgenual cingulate gyrus of the brain[3] and single cervical vagal nerve stimulation[4]).

On August 9-10, 2017, the American College of Surgeons (ACS), under the leadership of its Executive Director, David M. Hoyt, MD, hosted a Metabolic Surgery Symposium. This symposium included 12 formal presentations that were serialized in successive monthly editions of the *ACS Bulletin* from December, 2018 through June, 2019.[5] The symposium called attention to the reality that MS is influenced by place and race. For example, the population of Asian countries is more susceptible to T2DM at a lower body-mass index (BMI) than non-Asian populations, therefore requiring a different formulation for advocating MS intervention. The contributions of the ACS and the American Society for Metabolic and Bariatric Surgery (ASMBS) to metabolic surgery advocacy were reviewed, including unification of standards, increased safety and quality of care, and decreasing complications and cost, epitomized in the founding of the Metabolic and Bariatric Accreditation and Quality Improvement Program in 2012.[6]

On reflection, surgeons have achieved the introduction of a new surgical discipline for the present and for the future at a time when the realm of surgery has otherwise contracted. Incisional surgery has been made, for the most part, unnecessary by antibiotics and radiologic-guided intervention. Extended extirpative surgery has yielded to minimal resections accompanied by chemotherapy and radiation therapy. Reparative surgery will give way to prostheses, gene therapy, and preventive medicine. MS, on the other hand, opens an evolving future for surgeons, filled with new expectations and accomplishments. The cognitive attributes of imagination, exploration, and research integral to metabolic surgery add to possible avenues for surgeons to explore intellectually, in addition to their technical skills, in the world of medicine and health care.

Metabolic surgery for the treatment of severe obesity

-Henry Buchwald, MD, PhD

Obesity has deadly outcomes, shortens life expectancy, robs the afflicted of the pleasures of life, challenges the health care system, and is detrimental to a nation's gross domestic product. It is truly malignant, and this disease deserves to be called morbid obesity. Language is not a trivial matter. Words reflect reality and also shape reality. If we diminish the impact of obesity, we remove it from being a disease, truly a morbid disease, to being a social subject of diversity. We must, therefore, not be persuaded to substitute severe obesity for morbid obesity or the patient with obesity for the obese patient, thereby minimizing the therapeutic impact of MBS. We cannot sacrifice truth in language; such an acquiescence is a major disservice to our patients.

History of obesity

The documented history of obesity starts approximately 30,000 years ago with pocket-sized figurines of obese women. The most famous of these figurines, dated to approximately 25,000 B.C., is the "Venus of Willendorf," made out of limestone originating in Spain rather than in Austria where the statuette was discovered; we can thus assume it traveled for some purpose, whether as a fertility symbol, an idolization of beauty, an object of worship, or a totem for good fortune. There are many references to obesity in the Bible, essentially all derogatory. The fourth century monk, Evagruis Ponticus, characterized obesity as resulting from gluttony, 1 of the 7 deadly sins. A more rational perspective of obesity as an impediment to good health and

longevity was documented in the writings of ancient Greece, Egypt, and India. Hippocrates wrote extensively in condemnation of obesity (Hippocratic Corpus): "Corpulency is not only a disease, but the harbinger of others. Those who are constitutionally very fat are more apt to die quickly than those who are thin." For the past 1,000 years or so, obesity has at times been considered a sign of privilege, although sometimes also a subject of parody and derision. In at least 10 societies, the fattening of young girls and women to make them more desirable has been documented as a tribal custom.

Today the deadly disease of obesity has become a world pandemic. World Health Organization (WHO) data show that approximately 1 billion adults and children are morbidly obese, and more than 2 billion are overweight.[7] In the United States, the incidence of overweight and obesity is more than 65%; there is not a single state that has a less than 25% prevalence rate of obesity.[8]

Evolution of bariatric procedures

Well over 50 operations have been proposed and implemented for the management of morbid obesity, a testament to the vigor and imagination of its advocates. The first non-resectional bariatric surgical procedure was performed by Richard L. Varco in 1953, who never published his case. The operation was a jejunoileal bypass (JIB) with an end-to-end jejunoileostomy and separate drainage of the bypassed bowel to the cecum. This procedure was subsequently reported by Kremen, Linner, and Nelson in 1954.[9] Several JIB modifications followed, the most popular being the "14 to 4″ end-to-side reconstruction reported by Payne and DeWind.[10] Although highly effective, the JIB was associated with many complications, and, in the late 1960s, gave way to the gastric bypass, first introduced by Mason and Ito in 1966.[11] This procedure was modified to a stapled, undivided separation of the upper and lower pouch, with drainage of the upper pouch by a loop gastrojejunostomy by Alden in 1977.[12] In the same year, Griffen and colleagues[13] and Pories and colleagues[14] reported the first gastric bypass with a Roux-en-Y gastrojejunostomy (RYGB). Currently, a variation of a single anastomosis loop gastrojejunostomy is again finding favor.

Mason, always eager to simplify bariatric procedures and minimize their side effects and complications, next introduced gastroplasty. Two variants of the vertical banded gastroplasty (VBG) with a restricted vertical pouch held favor, and, in the 1990s, eclipsed the RYGB in the number of procedures performed, those with distal restriction by a Silastic ring[15] and those with a Marlex band outlet restrictor.[16] By the turn of the century, however, the VBG faded into near oblivion due to fairly ubiquitous weight gain and gastroesophageal reflux over time.

Scopinaro, from Genoa, Italy, returned to the intestinal bypass concept in the late 1970s but sought to avoid the static intestinal loop toxic effects of the original procedure by performing a subtotal gastrectomy with Roux limb drainage, at least 250 cm in length, anastomosed to a long biliopancreatic limb to form a common channel of 50 cm.[17] When this procedure crossed the Atlantic, it was transformed into the duodenal switch (DS), first by Picard Marceau, of Canada,[18] who performed a vertical sleeve gastrectomy with cross-stapling of the duodenum, and an approximately 100 cm common channel. Cross-stapling of the duodenum proved to be unstable and led to the biliopancreatic diversion/duodenal switch (BPD/DS) or simply the DS, by Hess and Hess in 1994, who divided the duodenum and performed a proximal duodenoileostomy.[19] Of the bariatric procedures, the BPD and the DS provide the greatest weight loss, are the most enduring in their weight response, and have the highest rate of comorbidity resolution, especially of T2DM. Nevertheless, they are performed relatively infrequently because they are difficult procedures necessitating the skills of a highly competent surgeon, and because they can cause long-term nutritional and hepatic complications requiring dedicated lifelong patient follow-up by a bariatric specialist.

The DS gave birth to the sleeve gastrectomy (SG) after an interlude of failed enthusiasm for the most purely anatomically restrictive procedure, the adjustable gastric band (AGB). The AGB succumbed to complications of band slippage and gastric perforation, as well as failure to main-

tain weight loss. In 2017, the SG became the most frequently performed metabolic/bariatric operation in the world. First advocated by Regan and colleagues in 2004,[20] it was popularized by Gagner[21] as the first stage of a DS, and, subsequently, as a standalone procedure. In order to avoid the relatively high incidence of upper gastric staple line leaks with the SG, Dolezalova-Kormanova and Martin Fried[22] devised the variant of gastric imbrication without resection.

Today a plethora of metabolic/bariatric operations are being proposed, among which are procedures that include electrode stimulations, single-anastomosis loop RYGB, and single-anastomosis variations of the DS, banded SG, and banded RYGB. In addition, there are several endoscopic suggestions for narrowing the gastric lumen by internal imbrication. Endoscopically inserted gastric balloons that work as gastric bezoars, and postprandial evacuation of the stomach by a surgically-placed gastrostomy tube have also been advocated for obesity management; they are, however, not truly metabolic procedures.

Weight outcomes of metabolic/bariatric surgery

There are literally thousands of papers in the peer-reviewed medical literature testifying to the marked weight loss achieved by metabolic/bariatric surgery. In 2004, we published the first systematic review and meta-analysis of bariatric surgery in 136 studies with 22,094 patients and an average percent excess weight loss (% EWL) of 61.2%.[23] In 2009, in a meta-analysis of 621 studies with 195,246 patients, we demonstrated increasing % EWL of 46.2%, 55.5%, 59.7% and 63.6% for GB, VBG, RYGB, and BPD/DS, respectively.[24] These findings have been confirmed by others, particularly by the publications of the Swedish Obesity Surgery Study[25] and in the International Federation for the Surgery of Obesity (IFSO) Registry results.

Weight regain after metabolic/bariatric surgery and occasional failure to lose significant weight have also been documented. Unbiased assessments, however, conclude that significant weight loss, greater than 50% EWL, has been maintained in more than 50% of metabolic/bariatric surgery patients. This statistic exceeds by far the less than 10% maintained weight loss achieved by diet and/or pharmaceuticals.

Complications of metabolic/bariatric surgery

The complications, in addition to weight regain, following metabolic/bariatric surgery have been well recorded in the literature. There are the universal postoperative complications of medical emergencies, leaks, hemorrhage, obstruction, and infection. In addition, there are the unique long-term problems of bowel obstruction due to internal mesenteric hernias, stenosis, and peptic ulcers.[26] The most common concern in long-term follow-up is nutritional deficiencies, such as iron-deficient anemia, and inadequate levels of vitamins and minerals.[27]

Mechanisms of obesity and metabolic/bariatric surgery

There are excellent data relating the tendency for obesity to genetics, however no epidemic or pandemic has ever been proven to be caused by a cataclysmic genetic mutation. Pandemics are the result of the introduction, or proliferation, of an uncontrolled agent into the environment and its effect on the metabolism of the population. The nature of this agent or factor is currently unknown. At this time, we attribute the obesity pandemic to an increase in a sedentary lifestyle and the availability of inexpensive fast food and sugars as primary vectors; they may, however, only be complementary factors.

In any event, we postulate that the cause of the obesity pandemic involves metabolic mechanisms and is, therefore, amenable to MS. Elucidating the mechanisms by which MS mitigates obesity may also elucidate the mechanisms for the etiology of obesity. MS is in the forefront of

this research. Our discipline has contributed enormously to our knowledge of the mosaic of neurologic patterns (eg, afferent vagal-hypothalamic pathways), intestinal hormones (eg, glucose-dependent insulintropic polypeptide, glucagon-like peptide-1, peptide-YY, etc.), and the contributions of alterations in the intestinal biomere and the composition of bile acids.

Metabolic/bariatric surgery in the COVID-19 or other pandemic eras

During a national health care crisis that will tax the capacity of health care workers and hospitals, it becomes imperative to cancel all elective surgery that can wait to be performed without threat to health or life. Metabolic/bariatric surgery is definitely not among these procedures. Once a metabolic/bariatric operation is decided upon, it belongs in the urgent category. It has been well documented that obesity, diabetes, and hypertension are primary risk factors for severity of, and mortality from, COVID-19.[28] In essence, these factors equate to the metabolic syndrome, a manifestation of the disease of morbid obesity, best and successfully treated by metabolic/bariatric surgery. It will be argued that weight loss per se takes time, but we must consider that the COVID-19 pandemic, and possibly future pandemics, will also last for a considerable period of time. In addition, T2DM reversal, "cure," occurs days after the operative metabolic/bariatric surgery procedure. Hypertension and hyperlipidemia also respond rapidly; blood pressure and blood lipid concentrations normalize within weeks. Although it is, of course, impossible to operate on the entire obese population of our nation, although that population might benefit from it, it is, however, feasible to operate on that fraction of patients most in need of the benefits of metabolic/bariatric surgery.

Once the health care emergency needs of a pandemic are met, a staggered, intelligent return to the operating room becomes feasible. In selecting the elective operative procedures for this affirmative transition, metabolic/bariatric surgery, for its prophylactic, curative, and life-saving effects, should be given priority.

Metabolic surgery for the treatment of type 2 diabetes mellitus

-Colston Edgerton, MD

As outlined in the proceeding sections, what was once colloquially referred to as "weight loss surgery" has appropriately evolved into the more inclusive and appropriate concept of MS, in large part because of the profound and durable effects it has been shown to have on the amelioration of T2DM. In this section, we review the known clinical outcomes of metabolic surgery for the treatment of T2DM and the proposed etiology and physiologic mechanisms for this phenomenon.

In 1999 the WHO published criteria for defining the metabolic syndrome (Table 1).[29] The American Association of Clinical Endocrinologists and The National Cholesterol Education Program's Adult Treatment Panel III Report (ATP III) have published similar definitions.[30,31] A significant contributor and highly morbid component of this syndrome is the development of insulin resistance associated with T2DM. In the early 1990s, during the open surgery era of bariatric surgery, long-term data began to show significant remission of T2DM in patients who underwent RYGB.[14, 32-34] A meta-analysis was published in 2009 that included 103 treatment arms and 3,188 patients with diabetes data following bariatric surgery. It demonstrated a 78.1% rate of complete resolution and 86.6% rate of resolution or improvement, which was similar for patients less than or greater than 2 years out from surgery.[34] There were no randomized controlled trials (RCT) comparing surgery and medical management for the treatment of T2DM until Dixon and colleagues[35] randomized 60 patients to either undergo laparoscopic adjustable gastric banding or medical management. Remission of T2DM was achieved by 22 (73%) in the surgical group compared to 4 (13%) of the conventional medical therapy group, with an odds ratio of 5.5 (95% CI 2.2-14.0). Several published RCTs comparing medical management to more contemporaneous

Table 1
The 1999 World Health Organization criteria for defining the metabolic syndrome. Adapted from reference 29.

- Insulin resistance as defined by one of the following:
  - T2DM,
  - Impaired fasting glucose,
  - Impaired glucose tolerance, or
  - Normal fasting glucose levels ≥110 mg/dL
- Any 2 of the following:
  - Hypertension
    - Antihypertensive medication, and/or
    - Systolic blood pressure ≥140 mm Hg, or
    - Diastolic blood pressure ≥90 mm Hg
  - Hyperlipidemia
    - Plasma triglycerides ≥150 mg/dL
    - HDL cholesterol ≤35 mg/dL in men or ≤39 mg/dL in women
  - Central obesity
    - Waist to hip ratio 0.9 in men and 0.85 in women
    - BMI ≥30 kg/m^2
  - Microalbuminemia
    - Urinary albumin excretion ≥20 mcg/min
    - Albumin/creatinine ratio ≥30 mcg/min

BMI, body-mass index; HDL, high density lipoprotein; T2DM, type 2 diabetes mellitus.

procedures followed. Mingrone compared RYGB or BPD to best medical therapy and found a remission rate at 2 years, defined as fasting glucose levels <100 mg/dL or a hemoglobin (Hb) A1c <6.5%, of 75% in the RYGB group, 95% in those undergoing BPD, and 0% in the medical arm.[36] Schauer and colleagues later randomized 150 patients 1:1:1 to RYGB, SG, or medical therapy. At 5 years follow-up, the primary endpoint of HbA1C < 6.0% off medications was met in only 5% of the patients in the medical therapy group compared to 29% in the RYGB cohort and 23% in those who had received SG.[37]

A recently published meta-analysis included 7 RCTs and 463 patients with at least 2 years follow-up published from 2008 to 2018.[38] T2DM remission was observed in 52.5% of patients after bariatric surgery compared to only 3.5% of patients with medical management, with a relative risk of 10 (95% CI 5.5-17.9, $P < 0.001$). Of the 4 studies that included 5-year follow-up, 27.5% of surgery patients and 3.8% of medical patients achieved remission targets. A meta-analysis of 4 RCTs comparing SG to RYGB found the remission rates at 5 years defined by HbA1c <6.5% to be 60% and 55%, respectively.[39] Although not an RCT, the Swedish Obesity Study is a prospective cohort study comparing 2010 patients who underwent bariatric surgery to 2037 matched controls.[40] Preoperative diabetes was diagnosed in 343 of the surgery patients and 260 patients in the control group. At 2 years, 72.3% of patients who had bariatric surgery achieved remission of diabetes compared to 16.4% of control patients defined as having a random blood glucose <110 mg/dL off all diabetic medications. At 15 years, these rates dropped to 30.4% and 6.5%, respectively. Although the procedures performed (61 AGB, 227 VBG, and 55 RYGB) do not reflect current patterns, these long-term data nonetheless support the findings of other randomized studies.

The antidiabetic effects of bariatric surgery were discovered serendipitously long before the pathophysiologic mechanisms were understood, which are still being elucidated today. Changes to insulin sensitivity and glucose metabolism are thought to occur independently of weight loss as evidenced by this being observed often within the first week after surgery. Interestingly, these weight independent changes in glucose and insulin metabolism are seen more frequently after RYGB, SG, and biliopancreatic diversion than after AGB.[38] Broadly speaking, the proposed mechanisms have been grouped into “foregut” theories predicated on the principle of bypassing the foregut as is seen with RYGB, and “hindgut” theories which are based on the more rapid delivery of substrate to the more distal small bowel.[41] Due to the observed effects following SG in which the foregut is not bypassed, many favor physiologic mechanisms based on hindgut

theories. One proposed mechanism is the increase in plasma levels of incretins, hormones that stimulate a decrease in blood glucose levels, thought to be due to earlier exposure of glucose rich substrates to the L cells of the more distal intestine, where GLP-1 and peptide-YY (PYY) are produced. Gastric wall tension after a gastric sleeve promotes bowel motility that may also deliver food more rapidly throughout the intestines. However, a study performed in rats that had undergone SG showed increased levels of GLP-1 with direct intraduodenal infusion of dextrose to suggest that the mechanism of mitigating T2DM after sleeve gastrectomy may be due to other hormonal changes irrespective of gut motility.[42] The alimentary limbs of patients who have undergone RYGB have been shown to exhibit increased expression of glucose transporters and an actual increase in the number of cells producing GLP-1.[43] Other proposed mechanisms that are the focus of intense research include improved hepatic insulin sensitivity, altered bile acid metabolism, and changes in the gut microbiome.

In conclusion, the anti-diabetic effects of the most commonly performed bariatric procedures today are profound compared to best medical therapy. For this reason, the International Diabetes Federation and the American Diabetes Association now recommend MS be considered for patients with BMI >30 kg/m^2 with poorly controlled T2DM on optimal medical therapy. Although some RCTs have included patients with class I obesity, including the STAMPEDE trial in which BMIs ranged from 27 to 43 kg/m^2, with an average of 37 kg/m^2,[37] additional randomized studies are needed in patients with lower BMIs. This will better inform the potential for MS to address diabetes resolution in an even broader patient population, given the successful outcomes consistently demonstrated in patients with moderate to severe obesity.

Metabolic surgery for the treatment of nonalcoholic fatty liver disease

-Colston Edgerton, MD

Nonalcoholic fatty liver disease (NAFLD) is being increasingly recognized as one of the most morbid conditions associated with metabolic syndrome. NAFLD exists along a spectrum of liver disease severity that can progress from fatty liver to non-alcoholic steatohepatitis (NASH) to cirrhosis if significant weight loss is not achieved to stabilize or reverse its course. In 2016, NASH became the second most common indication for liver transplantation in the United States and is the most common indication in Asian, Hispanic, and non-Hispanic white females.[44] This is in part due to the development of a medical cure for hepatitis C, but also a consequence of the increasing prevalence of morbid obesity and metabolic syndrome. NAFLD is estimated to be present in up to 90% of those with morbid obesity.[45] Within a decade, 25% of these patients will progress to NASH and one third of those will further progress to cirrhosis.[46] This is driven by the finding that 60% of hepatic lipid is generated from adipose tissue derived free fatty acids.[47] Steatosis is closely correlated with hepatic and systemic insulin resistance but remains sensitive to insulin-mediated lipogenesis. The pro-inflammatory environment and oxidative stress seen in lipid rich hepatocytes eventually leads to cell damage and apoptosis.

Intervening with MS prior to the development of advanced liver disease and cirrhosis may prevent significant morbidity and mortality as well as decrease health care costs. A comparative study of the National Inpatient Sample Database from 2004 to 2012 analyzed the outcomes of 18,618 patients who carried a diagnosis of NAFLD and morbid obesity. Of those patients, the 41% who underwent BS were shown to have a decrease in all-cause mortality as well as diagnosis of cirrhosis with a RR of 0.08 (95%CI 0.03-0.2) and 0.16 (95% CI 0.13 - 0.19), respectively.[48] Rates of cirrhosis were 1.46% in the surgery cohort compared to 11.08% in the non-surgery cohort. Despite these data, the percentage of patients who underwent BS in this patient population decreased by 5.94% over the course of the study period. A more recent review of a large insurance administrative claims database identified 2942 patients diagnosed with NAFLD who also underwent bariatric surgery, matched to 5884 controls who were diagnosed with NAFLD but did not undergo surgery. After 2 years of follow-up, the relative risk of being diagnosed with cirrhosis in the surgery group compared to controls was 0.31 (95% CI 0.19 - 0.52).[49]

Although the benefits of halting the progression of NAFLD to steatohepatitis and cirrhosis are clear, perhaps the most remarkable finding is that MS can even reverse the most advanced stages. A meta-analysis of 15 studies containing paired liver biopsies before and after BS showed improvement or resolution of steatosis in 91.6%, steatohepatitis in 81.3%, and fibrosis in 65.5% of patients.[50]

Unlike other components of the metabolic syndrome, the degree of liver injury does not directly correlate to the severity of obesity.[51] The gold standard for diagnosis of NAFLD is a liver biopsy, with 73% of biopsy proven fatty liver disease being undiagnosed by serum liver function tests alone.[52] The Fibrosis-4 (FIB-4) and NAFLD Fibrosis Score (NFS) estimate advanced fibrosis, but screening for earlier stages of disease is more difficult. When selected for the right patients, ultrasound or magnetic resonance imaging (MRI) elastography have proven diagnostic value, but are less commonly used as a readily available, inexpensive screening method. Although NAFLD is present in a striking percentage of patients with morbid obesity, it is for this reason that other comorbid conditions associated with metabolic syndrome, such as diabetes and hypertension, are more easily screened for and diagnosed. As such, the potential therapeutic benefit of MS may be underestimated in population-based studies. Furthermore, although there are experimental treatments being investigated, there are no approved medical therapies for NAFLD. In contrast to viral hepatitis with new advanced anti-viral therapies, the only treatment for fatty liver disease is surgical. For these reasons, there will be an increasing importance placed on the role of MS, even outside of the established BMI cutoffs to address this evolving public health issue.

Metabolic surgery for the treatment of obstructive sleep apnea

-Scott A. Shikora, MD

Obstructive sleep apnea (OSA) is the repetitive reduction or cessation of breathing caused by upper airway obstruction. This often results in hypoxia and deranged sleep. OSA is uncommon in the general population, with an incidence of only 2% to 4%.[53] OSA occurs at a dramatically higher rate for individuals whose BMI is greater than 25 kg/m^2. OSA is generally thought to be under diagnosed because not all prospective bariatric surgery candidates are screened for OSA. Studies that evaluated all surgical candidates have reported even higher incidences. For example, de Raaff and colleagues[54] performed polysomnography on a cohort of patients preparing to undergo BS, whose mean BMI was 44.1 kg/m^2. These investigators found that 59.9% of their patients had OSA.[54] One third of patients had severe OSA.

The symptoms of OSA include poor sleep, loud snoring, daytime drowsiness, and neurocognitive disorders. In some patients, OSA may be asymptomatic. Untreated, individuals with severe OSA are at risk for cardiovascular issues such as hypertension, pulmonary hypertension, myocardial infarction, respiratory failure, and even sudden death.[55,56]

The conventional non-invasive treatment for OSA is the use of continuous positive airway pressure (CPAP) or bi-level positive airway pressure (BiPAP) at night when sleeping to prevent the upper airway collapse.[57–59] Although CPAP is effective for improving sleep and reducing mortality, patients are often poorly compliant with its use secondary to discomfort with the appliance or difficulty adjusting to wearing it.[60, 61]

Various non-bariatric surgical procedures are available. They all attempt to remove excess pharyngeal tissue to open up the airway. None of these treatments are 100% effective.[60] Uvulopalatopharyngoplasty, the removal of excess soft tissue of the posterior palate, uvula, and pharynx, is a commonly performed procedure, but is not often effective for patients whose BMI is 35 kg/m^2 or greater.[62]

It has been long recognized that obesity is commonly associated with OSA. There is a positive correlation between increasing BMI and the severity of sleep apnea. In fact, a 10% increase in weight is associated with a 6-fold increased likelihood of developing moderate to severe OSA.[64]

Table 2
Obesity associated cancers. Adapted from references 74 and 75.

Esophagus (adenocarcinoma)
Breast (postmenopausal)
Colorectal
Endometrial
Gallbladder
Gastric
Kidney
Multiple myeloma
Ovarian
Pancreatic
Liver
Meningioma
Thyroid

Table 3
Estimated new cancer cases, 2020 (adapted from American Cancer Society).

Breast	279,100
Lung and bronchus	228,820
Prostate	191,930
Colorectal	147,950
Melanoma	100,350
Urinary bladder	81,400
Non-Hodgkin lymphoma	77,240
Kidney and renal pelvis	73,750
Uterine corpus	65,620
Leukemia	60,530

In addition, weight loss by any means, even modest weight loss, results in improvements or resolution of OSA.[63]

There is a large body of literature that has reported that OSA improves, and often even resolves after bariatric surgery.[64-66] The severity of the OSA prior to bariatric surgery may influence the degree to which the OSA improves after surgery.[67] In addition, as not all cases of OSA are related to excess pharyngeal tissue, the rate of improvement or resolution of OSA after MBS is not 100% with weight loss.[67] Furthermore, the amount of weight loss achieved does not seem to significantly correlate with the extent of the improvement in the OSA.[66] As with other obesity associated medical conditions, patients who had improvement or resolution of their OSA after MBS, may experience a recurrence of their OSA with weight regain.[68] Despite these issues, MBS is still considered the treatment of choice for patients with BMI of 35 kg/m^2 or greater who suffer from OSA. This recommendation was supported by the ASMBS based on the review and interpretation of the existing literature by their clinical issues committee.[69]

Metabolic surgery for the treatment of cancer

-Scott A. Shikora, MD

It has long been recognized that patients with excess adiposity are at greater risk of developing cancer.[70-73] In fact, there are 13 malignancies (Table 2), that are closely associated with obesity. These tend to be the hormonally-sensitive cancers.[74,75] In fact, 40% of all new cancers were those associated with obesity (Table 3).[75] Furthermore, 55% of cancers in women and 24% in men are among the obesity associated cancers.

Weight reduction has been shown to reduce the likelihood of developing cancer and improve the outcome for those patients who had cancer.[76, 77] To investigate these observations, Adams and colleagues,[77] reviewed a database from a previous retrospective cohort mortality study that

compared 9,949 patients who had undergone gastric bypass surgery between 1984 and 2002 to a matched control group of 9,628 participants with obesity who did not undergo surgery. Consistent with previous reports, after a follow-up of more than 24 years (mean, 12.5 years), the investigators found that the incidence of cancer was 24% lower in the gastric bypass patients ($P = 0.0006$). However, this difference was seen only in women. There was no significant difference in the incidence of cancer in men or those patients with non-obesity related cancers. This observation may be explained by the greater number of women in the trial than men and the high prevalence of the obesity-related cancers such as endometrial and breast cancer. In fact, there was a significant decrease in uterine cancer in the surgical group compared with the control group ($P < 0.0001$). Similarly, Trentham-Dietz and colleagues reported that increasing BMI was associated with an increased risk of developing endometrial cancer and there was a 30% reduction in the risk for developing endometrial cancer for women who sustained weight loss.[78] In 2 separate but similar studies involving systematic reviews of the medical literature, Winder and colleagues found that patients who had bariatric surgery reduced the incidence of endometrial cancer (0.4% vs 1.4%, $P < 0.001$)[79] and reduced the incidence of breast cancer (1.1% vs 2.6%, $P < 0.001$).[80] Overall, there was a 38% reduction for the obesity-related cancer ($P < 0.0001$) as reported.[81]

Most significantly, Adams and colleagues observed a 46% reduction in cancer deaths for those patients who underwent gastric bypass surgery.[77] Schauer and colleagues demonstrated similar findings and stated that every 10% of body weight reduction resulted in a 14% reduction in cancer risk.[76] The decrease in cancer morality was thought to be due to the decreased risk of developing cancer due to the weight loss achieved by the surgery and not due to anything specific about the operative procedure itself.[76]

There are several other published reports of reduced cancer incidences with weight loss, including a publication reporting from the ongoing Swedish Obesity Trial. Sjostrom and colleagues have been prospectively following 2010 patients who underwent bariatric surgery and a matched control group of 2037 participants who did not have surgery. After a mean follow-up of 10.9 years, these investigators reported 129 deaths in the control group and significantly fewer deaths, 101, in the surgical group ($P = 0.04$). There were 47 cancer deaths in the control group versus only 29 cancer deaths in the surgical group.[81]

Lastly, Reeves and colleagues, using the Million Women Study found that BMI influences both the incidence as well as the outcome for a wide range of cancers.[72] Although there was significant heterogeneity, as weight increased, so did the risk of developing cancer.

Obesity also has a negative effect on cancer treatment.[82, 83] Abe and colleagues reported that women with obesity who develop breast cancer had larger primary tumors, higher rates of lymphatic spread, and overall worse survival when compared with normal weight women.[82] The reason for this is multifactorial. Tumor biology, delay in diagnosis, underlying health issues, psychosocial issues, and the challenge of performing surgery on patients with excessive adipose tissue all contribute. In addition, the treatments (surgery, radiation, and chemotherapy) may all be less effective.

As all surgeons know, the patient with severe obesity poses greater perioperative risks than the patient without obesity. The larger body and excess of adipose tissue makes the technical aspects of the surgery more difficult, resulting in longer operating time, a higher likelihood for technical problems such as bleeding or leak, and a greater possibility of having to convert a laparoscopic or robot case to an open laparotomy. In addition, the patient's underlying health issues such as hypertension, diabetes, OSA, heart disease, etc. also increase the likelihood of perioperative complications such as infections, heart attacks, strokes, deep vein thrombosis, etc.

Metabolic surgery for the treatment of kidney disease

-David Harris, MD, PhD

The incidence of chronic kidney disease (CKD) is increasing worldwide and now affects nearly 10% of the world's population. The interplay of obesity and the development of CKD is com-

plex.[84] Although obesity is a potent contributor to the development of CKD and hastens the transition from CKD to end stage renal disease (ESRD), there are multiple studies which describe an "obesity paradox" whereby an elevated BMI is associated with improved survival in patients with ESRD on dialysis.[85] Nevertheless, there is substantial literature linking obesity with the development of CKD, ESRD, and poor renal transplant outcomes.

Obesity causes glomerular hyperfiltration, leading to increased sodium reabsorption and impaired natriuresis. This results in volume expansion through activation of the sympathetic nervous system and renin-angiotensin-aldosterone system. In addition, obesity associated inflammation, lipotoxicity, and oxidative stress induces renal dysfunction.[86] These effects also increase the risk for hypertension, which will be discussed in the next section.

Glomerular hyperfiltration and obesity-induced renal inflammation leads to the development of obesity-related glomerulonephritis, which has increased over the past 4 decades.[84] Obesity is associated with a nearly 25% risk of CKD and in patients with a BMI greater than 30 kg/m^2 or 40 kg/m^2 there is 3-fold and 7-fold higher risk of developing ESRD, respectively, when compared to normal weight individuals.[87] Additionally, aside from the direct effects of obesity on renal function, obesity induces metabolic syndrome, which is linked to the development of CKD. Nearly 50% of patients with T2DM will end up developing CKD and this risk is compounded in individuals with obesity and hypertension.[84]

Although obesity may offer survival advantage to patients who have progressed to ESRD on dialysis, with each successive obesity class, patients have a significantly reduced likelihood of obtaining a renal transplant, which offers a clear survival advantage over remaining on dialysis.[88] In fact, according to surveyed members of the American Society of Transplant Surgeons, a BMI of 38 and 41 kg/m^2 are relative and absolute contraindications, respectively, to transplantation in most programs. Obesity not only makes the technical aspects of transplantation much more difficult, but also puts patients at higher risk for postoperative surgical site infections, hernia formation, and allograft rejection.[89]

Weight loss has been shown to be protective against the progression to CKD and in the success of renal transplantation in patients with obesity. Thus, it would stand to reason that metabolic operations, which have profound effects upon adiposity, inflammation, T2DM, and weight, would have a substantial effect upon the development of CKD/ESRD and transplantation in at-risk patients.

Imam and colleagues showed that among patients with a BMI greater than 35 kg/m^2 and stage 4 or 5 CKD, SG and to a greater extent RYGB led to sustained, 3-year improvement in the estimated glomerular filtration rate (eGFR) by nearly 10 mL/min/1.73 m^2 as compared to matched, non-surgical controls. Interestingly, these changes seemed highly linked to weight loss, with an overall increase in eGFR by 0.21 mL/min/1.73 m^2 for every 10 pounds lost.[90] Others have shown that following RYGB, patients with obesity and T2D are greatly protected from severe renal disease (HR 0.56) regardless of baseline renal function.[91] Aside from changes in eGFR, metabolic operations have been further associated with improvements in the pathogenesis of obesity-induced glomerulonephritis with reduced hyperfiltration and albuminuria.[92-94]

Despite these demonstrated improvements, designing studies to test how the obesity paradox affects the decision to proceed with MS in patients with CKD remains elusive. Using Markov modeling to simulate patient outcomes based on existing published data, Choudhury and colleagues sought to address this issue by answering 2 main questions: (1) in patients with CKD3 and obesity, which class of obesity would benefit from MS and (2) in patients with ESRD and a BMI greater than 45 kg/m^2, which metabolic operation would be the most beneficial.[95,96] Their modeling revealed that RYGB and SG improved survival for patients with class II and III obesity but not for patients with class I obesity.[95] And, for patients with morbid obesity, RYGB had higher rates of transplantation and improved long-term survival with an additional 1.3 and 2.6 years of life compared with patients who underwent SG and medical weight loss, respectively.[96]

Although this study was suggestive that RYGB could offer the most benefit, a recent large retrospective cohort study of 1597 patients by Sheetz and colleagues showed that multiple forms of MS (eg, RYGB, SG, lap banding, or DS) were associated with a combined lower all-cause mor-

tality at 5 and 7 years (25.6% vs 39.8%; HR 0.69) and a 13% increase in the transplantation rate amongst patients with ESRD.[97]

Mirroring the trends in the general population, SG has fast become the most common operation performed in patients with obesity and ESRD (84% in 2016), owing to its improved safety profile and profound metabolic benefits.[98] SG has been shown to improve transplant candidacy by leading to sustained improvements in patient weight and comorbidities. Furthermore, compared to weight-matched controls, patients who underwent SG prior to transplant had reduced delayed graft function (5% vs 20%) and post-transplant readmissions.[99] Importantly, transplant waitlist mortality was also improved after SG compared to the general population (1.8 vs 7.3 per 100 patient-years), suggesting that the benefits of SG extend beyond the realization of transplantation.[100]

Although the interactions between obesity and CKD, ESRD, and renal transplantation are complex, there is convincing evidence that patients with a BMI greater than 35 kg/m^2 have profound benefits from MS, with stabilization and/or improvement in eGFR, reduced obesity-related glomerulonephritis, improved transplant candidacy, improved post-transplantation allograft function, and reduced mortality. As such, patients with a BMI greater than 35 kg/m^2 and CKD should be considered for surgery. Additionally, those patients with ESRD nearing or on HD would benefit from early referral for MS because they will be near the top of the transplant waitlist by the time their BMI is at a level safe for transplantation. Patients should be offered the metabolic operation that is best suited to their individual needs; however, SG is likely the first line operation for most patients within this population.

Metabolic surgery for the treatment of hypertension

-David Harris, MD, PhD

The pathogenesis of hypertension in obesity is not completely understood. However, obesity appears to contribute indirectly to hypertension through renal injurious means and directly via increasing sympathetic drive. Obesity leads to a deleterious cycle of glomerular hyperfiltration, increased sodium reabsorption, volume expansion, increased mean arterial blood pressure, and glomerular injury. This is exacerbated further by obesity associated chronic induction of the renal sympathetic nervous system.[101]

Weight loss is known to reduce these effects and a medical weight loss program can reduce hypertensive medication burden in patients with a BMI greater than 27 kg/m^2 despite only modest weight loss.[102] Furthermore, weight loss in patients with a BMI between 26 and 37 kg/m^2 at risk for hypertension (elevated diastolic blood pressure but systolic blood pressure $<$ 140 mm Hg), is protective against the development of hypertension at 36 months compared to those without weight loss (relative risk, 0.79 [CI, 0.65 - 0.96]).[103]

In a multicenter RCT of RYGB versus medical management for the treatment of metabolic syndrome (obesity, diabetes, hypertension, hyperlipidemia), Ikramuddin and colleagues showed that patients who underwent RYGB were much more likely to reach the composite end point of HbA1c $<$7%, serum low-density lipoprotein (LDL) $<$100 mg/dL, and systolic blood pressure $<$130 mmHg (28 vs 11%). The difference in outcome was driven by a reduction in HbA1c, but patients following RYGB had a lower mean systolic and diastolic blood pressure compared to those randomized to medical therapy.[104] Five-year follow-up data showed that achievement of the composite end point was more likely in patients who had undergone RYGB. (23% vs 4%).[105]

The GATEWAY trial is the largest randomized controlled study to date focused solely on hypertension after MS. The authors enrolled 100 patients without diabetes and with a BMI of 30 to 39.9 kg/m^2 and hypertension (defined by $\geq$ 2 medications at maximum dose or $\geq$ 3 at moderate doses) to undergo RYGB or intensive medical therapy. One-year outcomes showed that when compared to medical therapy, patients that underwent RYGB were much more likely to achieve $\geq$ 30% reduction in anti-hypertensive medical use (12.8 vs 83.7%) and complete remission of their hypertension (0 vs 51%). Importantly, as expected, patients following RYGB had greater re-

duction in BMI (27 vs 36 kg/m^2), increased GFR, and reduced serum LDL.[106] Again, there was incredible preservation of these effects at 3 years, with 72.7% (vs 12.5%) and 40.9% (vs 2.1%) of patients having achieved ≥30% reduction in anti-hypertensive medication use and remission of hypertension following RYGB, respectively.[107]

Not unexpectedly, SG has also been shown to have a significant impact on obesity-related hypertension, with nearly 58% having resolution of and 75% improvement in their hypertension at 1 year follow-up.[108] Some retrospective comparative studies of SG and RYGB and the SLEEVEPASS RCT show that RYGB is superior to SG in terms of hypertension control and remission. In the latter, RYGB was associated with a 51% and SG a 29% hypertension remission rate at 5 years.[109] However, in a large retrospective study of 7000 patients with obesity and hypertension, there were no differences between the operations. Within this cohort (all privately insured), hypertension remission occurred in 84% of patients with 13% having recurrence at a median time of 306 days. As in the case with diabetes following surgery, the number of anti-hypertensive medications prior to surgery was a predictor of remission.[110]

Nonetheless, it is clear that the profound effects of MS on weight loss and renal function have an added effect on hypertension in patients with obesity. Patients should be counseled on their surgical options and the appropriate operation should be chosen based on a shared decision between the surgeon and patient.

Metabolic surgery for the treatment of heart disease

-Scott A. Shikora, MD

Several recently published studies[111-115] have demonstrated that overweight and obesity are independent risk factors for cardiovascular disease (CVD) including coronary artery disease, myocardial infarction,[113,114] congestive heart failure,[115] and atrial fibrillation.[118] For example, Khan and colleagues demonstrated in a study of 190,672 in-person examinations, that compared with normal weight individuals, the lifetime CVD risks were significantly higher in patients who were overweight (BMI 25.0-29.9 kg/m^2), obese (BMI 30.0-39.9 kg/m^2), and morbidly obese (BMI ≥40.0 kg/m^2). In fact, adults with obesity had an earlier onset of CVD, lived more years with CVD, had more CVD events, and had an overall shorter life expectancy compared with normal weight adults.[112] In addition, the higher the BMI, the stronger the association with heart failure. These findings were consistent whether abdominal adiposity was estimated by BMI, waist-to-height ratio, or waist circumference measurements.[113,114] In a multination case-control study, Yusuf and colleagues found a strong correlation between waist-to-hip ratio and myocardial infarction.[114] Furthermore, obesity was found to increase the risk of death from all causes but in particular, CVD.[115] Calle and colleagues prospectively studied more than 1 million adults from the Cancer Prevention Study II. Patients were placed in 12 categories based on BMI. The investigators found that the relative risk of mortality increased with increased BMI. In men, the relative risk of death from CVD was 2.90 (95% confidence interval, 2.37 - 3.56).[115]

Obesity has also been demonstrated to be a risk factor for the development of atrial fibrillation.[116] Wang and colleagues studied 5282 participants in the Framingham Heart Study. After a mean follow-up of 13.7 years, 526 participants developed atrial fibrillation. These investigators found that the risk of atrial fibrillation increased with increasing BMI, with a 4% increase in risk for each unit increase in BMI. Adjusted hazard ratios for atrial fibrillation associated with obesity were 1.52 (95% CI, 1.09-2.13, $P = 0.02$) and 1.46 (95% CI, 1.03-2.07, $P = 0.03$) for men and women, respectively. This risk was shown to be related to left atrial diameter which was significantly greater in men with obesity compared to men with a normal BMI (4.4 ± 0.5 cm vs 4.1 ± 0.4 cm, $P < 0.001$).

Excess adiposity is a risk factor for heart failure in part due to unfavorable remodeling of the heart itself.[111] These patients are at risk for left ventricular hypertrophy and left atrial enlargement.[117]

The disease of obesity is very diverse. Patients suffering from obesity vary greatly in the presence or absence of morbid conditions and when present, the severity of these diseases. Although some patients suffer greatly, others have few or none of the associated conditions and would be considered "fit." However, in a study of these patients, Stevens and colleagues found that patients with obesity that were fit, as defined by performance on a standard treadmill test, still had a greater risk of all-cause mortality and CVD.[118] The relative risk of CVD in these patients was highest in the unfit patients with obesity, and lowest in the fit patients of normal weight. The fit patients with obesity were somewhere in between. The investigators concluded that "fitness and fatness are risk factors for mortality, and that being fit does not completely reverse the increased risk associated with excess adiposity."

Having obesity as a young adult or adolescent has serious consequences for the development of CVD at a later age.[119] Hendrickson and colleagues studied 1 million young men in the Swedish Military Conscription Register. Young men with obesity were 2.5 to 4 times more likely to get granted disability pensions due to chronic cerebrovascular diseases and ischemic heart disease (HRs between 2.57 and 4.35) and 6 times more likely due to heart failure (HR 600; 95%, CI 2.97-12.11) compared with normal weight adolescents. This was particularly true for the unfit young adult with obesity.

There is a growing body of literature that has demonstrated that BMS improves cardiac function. It is unclear, however, whether these improvements are solely the result of the surgery-induced weight loss or whether there are other factors in play as well. Using data from the much acclaimed Utah Obesity Study, Owan and colleagues,[117] demonstrated that at the 2-year follow-up, in addition to meaningful weight loss, patients who underwent BMS also benefitted from significant reductions in waist circumference, systolic blood pressure, heart rate, triglycerides, LDL cholesterol, and insulin resistance and an increase in high-density lipoprotein (HDL) cholesterol. Additionally, they observed an actual reversal of the cardiac remodeling including a reduction in left ventricular mass index and right ventricular cavity area. There was a decrease in interventricular septum thickness, posterior wall thickness, and relative wall thickness. This resulted in improved heart function.

Metabolic surgery for the treatment of hyperlipidemia

-Henry Buchwald, MD, PhD

It is well known that metabolic/bariatric surgery markedly lowers serum total cholesterol, and, in particular, the LDL fraction. The responsible metabolic/bariatric surgery operative procedures are both restrictive and malabsorptive by the old terminology, primarily focused on the stomach (SG) or on a short common intestinal segment (BPD/DS), and all do so by metabolic mechanisms not yet fully identified. This response is, of course, cardinal for the mitigating effect of metabolic/bariatric surgery on heart disease, part of the spectrum of metabolic/bariatric surgery metabolic outcomes.

There is one MS operation that was developed specifically for the treatment of the hyperlipidemias and is still today the most effective therapy for lowering blood lipids: the partial ileal bypass.

Circulating cholesterol consists of synthesized cholesterol, formed primarily in the liver, plus ingested cholesterol, and because bile acids are the primary end products of cholesterol metabolism, interference in the cholesterol and bile acids enterohepatic cycles should reduce the circulating plasma cholesterol concentration. Working in the laboratory, from 1962 to 1963, I was able to demonstrate that the terminal ileum is the primary site for the absorption and reabsorption of both cholesterol and bile acids; that the partial ileal bypass in hypercholesterolemic rabbits and pigs significantly lowered the plasma cholesterol concentration; and that in 7 human volunteers who had previously undergone a partial ileectomy for benign causes, the plasma total cholesterol concentration was exceptionally low (130 mg/dL). On May 23, 1963, I performed the

first partial ileal bypass operation on a 14 year old boy with severe familial hypercholesterolemia and coronary heart disease.[120]

In later years, in human subjects, in our metabolic laboratory, we showed that the partial ileal bypass operation would, on an average, lower cholesterol absorption by 60%, cause a compensatory increase in fecal steroid excretion of 380%, a compensatory increase in cholesterol synthesis of 450%, with a cholesterol turnover rate increase of 300%. Most importantly, by dual isotope analyses, we ascertained that the cholesterol pools were reduced by 35%, including the less freely miscible pool of arterial plaque cholesterol.[121] The side effects of the partial ileal bypass were relatively minimal and consisted of an increase in bowel movements to approximately 3 to 4 daily, with occasional gas-bloat syndrome, and the generation of oxalate kidney stones, preventable by oral citrate administration.

In 1972, Richard L. Varco and I submitted our grant application to the National Heart Lung and Blood Institute (NHLBI) of the National Institutes of Health (NIH) for what was to become the Program on the Surgical Control of the Hyperlipidemias (POSCH) trial, a 65 million dollar effort in 4 geographically diverse institutions, involving 838 survivors of a single myocardial infarction documented by electrocardiograms and changes in enzyme values (417 diet controls, 421 diet instruction plus partial ileal bypass). The POSCH trial was the first NIH-funded RCT that utilized a MS procedure as the intervention modality. The results of the POSCH trial were presented at a special session of the American College of Surgeons in October of 1990, and first published in the New England Journal of Medicine concurrently with the meeting.[122]

When compared with the control group at 5 years, the surgery group had a total plasma cholesterol level 23.3% lower, a LDL cholesterol level 37.7% lower, and a HDL cholesterol level 4.3% higher (all $P < 0.05$). Overall mortality and mortality due to coronary heart disease were reduced, however it took another 5 years for this outcome to become statistically significant at the $P = 0.05$ level. The overall mortality in the surgery subgroup with an ejection fraction greater than 50% was 36% lower than in the control group, and this finding was statistically significant ($P = 0.021$). The combination of 2 endpoints (death due to coronary heart disease and confirmed nonfatal myocardial infarction) was 35% lower in the surgery group ($P < 0.001$). During follow-up, 137 control-group and 52 surgery-group patients underwent coronary artery bypass grafting ($P < 0.0001$). In addition, peripheral vascular disease was reduced in the partial ileal bypass group, in terms of intermittent claudication (71 events in controls, 52 in the intervention group, $P = 0.038$) and Doppler assessment (119 in controls, 126 in the intervention group, $P < 0.01$).

The POSCH trial permitted us to obtain sequential coronary arteriograms at baseline and 3, 5, 7, and 10 years after randomization. The percentage of patients with disease progression increased in both study groups but was consistently higher in the control group. At each follow-up interval, the difference between the control and surgery groups in the percentage of patients with definite disease progression was significant ($P < 0.001$). There was definite and statistically significant ($P < 0.05$) evidence for plaque regression 5 and 7 years after randomization.[123]

The POSCH study patients were followed for up to 30 years, and some longer. During that span of time, a significant ($P < 0.05$) increase in life expectancy was found in the partial ileal bypass group.[124]

Although the clinical utilization of the partial ileal bypass operation today is minimal due to the development of the statin drugs, this metabolic procedure and the POSCH trial represent the first proof of the converse of the lipid/atherosclerosis hypothesis, namely that not only is hypercholesterolemia a major risk factor for atherosclerotic coronary and peripheral vascular disease but that lowering the plasma cholesterol markedly reduces this liability with respect to symptomatology and mortality.

In a 2017 reassessment of the POSCH database, we ascertained another metabolic outcome of the partial ileal bypass procedure. Over approximately 30 years following trial randomization, the control group incidence of developing T2DM was 2.7-fold that of the partial ileal bypass group. This finding was achieved with essentially minimal weight loss.[125]

In conclusion, partial ileal bypass represents an operation specifically designed and researched for the amelioration of hypercholesterolemia. Contrary to MBS, the mechanisms for the processes and outcomes of partial ileal bypass have been ascertained. These findings may be

Table 4
Clinical staging of traumatic brain injury.

Stage I: Attention deficit, short-term memory difficulties, confusion, disorientation, dizziness, headaches, aggressive tendencies
Stage II: Social instability, impulsive behavior, mood swings, executive dysfunction, language difficulties, suicidality
Stage III: Cognitive impairment, explosivity, memory loss, visio-spatial difficulties, depression
Stage IV: Severe depression, movement disorders, tremors, severe memory loss, paranoia, dementia, suicidality

beneficial in the elucidation of the metabolic mechanisms responsible for the outcomes of other MS procedures.

Metabolic surgery for the treatment of traumatic brain injury and chronic traumatic encephalopathy

-Henry Buchwald, MD, PhD

Preceding sections have highlighted established examples of MS. As we proceed into the future, new, often previously not imagined, employments of the discipline of MS are discovered. On the cusp of arrival is MS for the treatment of traumatic brain injury (TBI) and chronic traumatic encephalopathy (CTE).[126]

Of the multiple named diseases of neurocognitive impairment, the etiology of only a few are known. We have risk factors and brain pathology for Alzheimer's disease but no agreed upon mechanism of causation. Two exceptions are post cerebrovascular accident vascular dementia secondary to ischemic brain damage, and TBI as a result of a devastating concussion or lesser multiple concussions. The terminal outcome of TBI is the dementia and early death from CTE, a disease definitively diagnosed today only at autopsy with no premortem signature marker.

TBI and CTE have been present in humankind since caveman days, with the advent of civilization often a subject of fiction and non-fiction literature. Historical descriptions of CTE can be found in ancient Egyptian papyruses (eg, the Edwin Smith Papyrus of 3,000 B.C.). The prevalence of TBI and CTE has not been well-documented. The problem certainly exists in other contact sports (eg, soccer, boxing, ice hockey), in the military (eg, blast injuries), and in the general population. These processes have come to the forefront in the last decade due to the publicizing of multiple early deaths in former National Football League (NFL) players. In 2005, Omala and colleagues published the first autopsy report defining CTE by the deposition of tau protein neurofibrillary tangles in the depth of brain sulci.[127] In 2017, Mez and colleagues, in an autopsy series of 110 former NFL players demonstrated CTE tauopathy in 110 of 111 (99%).[128] This autopsy finding was also existent in college football players who died young (48 of 53, [91%]).[129]

Failing the availability of a signature marker for the diagnosis of TBI and progression to CTE, the Centers for Disease Control (CDC) has resorted to clinical staging (Table 4). The time course for progression of TBI to CTE is prolonged, possibly up to 10 years or longer before the earliest brain pathology becomes manifest, and probably more years before the process becomes clinically evident. Therefore, a window of opportunity exists for acceleration of the process, as well as for mitigation and delaying or preventing clinical expression.

Known factors for acceleration include the presence of elevated inflammatory markers (eg, tumor necrosis factor, IL-6),[130] cardiovascular disease and risk factors,[130,131] and obesity.[132] Several authors have defined the relationship between obesity, progressive TBI, and CTE. Obesity reduces cognitive and motor functions across the lifespan[133]; obesity is associated with brain atrophy[134]; obesity is associated with executive dysfunction[135]; and obesity disrupts neurocircuitry, neuroendocrine activity, neurotransmitter metabolism and activity, and neurogenesis.[136]

There are at least 35 references in the peer-reviewed literature demonstrating that MBS is appropriate therapy for TBI and early CTE during the window of opportunity from initiation (concussion) to clinical asseveration. At 24 weeks after MBS, cerebral metabolism in obese patients improved, as well as executive function, in association with favorable changes in metabolic

and inflammatory parameters.[137] In 10 out of 10 studies in a systematic review, there was documented improvement in a neurocognitive domain after MBS.[138] And MBS improved cognitive function for up to 3 years, a long time span for progressive TBI.[139]

Why does MBS affirmatively impact TBI/CTE? Weight loss per se is probably beneficial. The metabolic perturbations secondary to MBS may play an independent, substantial role in promoting therapeutic outcomes. These changes include decreased levels of inflammatory markers, increased adiponectin levels, release of GLP-1 hormone, favorable alterations in the gut microbiome, and changes in bile salt composition. It has also been shown that white and gray matter brain integrity is benefitted by MBS.

In summary, today there is no known therapy to prevent, retard, or reverse TBI/CTE. None whatsoever. MBS has the potential to be the first effective treatment for TBI/CTE in the sizable obese cohort of this deadly neurocognitive impairment.

Metabolic surgery role for organ transplantation patients

-Colston Edgerton, MD

Organ transplant recipients and those with end stage organ disease were historically felt to be too high risk for consideration of MS. With advances in operative technique and a decline in morbidity and mortality, this paradigm has shifted. For those patients in need of an organ transplant, but denied due to severe obesity, MS may result in sufficient weight loss to be listed for transplantation. In this way, MS can extend life expectancy in this unique population through means not directly associated with its metabolic effects. In this section, we focus on the role of MS in patients with end stage renal, liver, and cardiac disease.

Although there are numerous etiologies for ESRD, diabetes and hypertension are among the leading causes in the United States. Given their association with metabolic syndrome, it is no surprise that as many as 20% of patients with ESRD in need of kidney transplantation (KT) are obese and meet criteria for MS.[140] Morbid obesity has been shown to be correlated with inferior outcomes following KT, including graft failure, delayed graft function, new onset diabetes after transplantation (NODAT), and death.[141] Many transplant centers and surgeons are less likely to accept organs from patients with severe obesity, which has resulted in BMI being inversely correlated to time on the renal transplant waiting list.[142] MS in this patient population has not been widely adopted in the past because of the increased 30-day adverse events associated with the concomitant cardiovascular disease and uremic platelet dysfunction, as well as the well-described "obesity paradox," in which improved survival is seen in dialysis dependent (DD) patients with higher BMI.[143,144] Nonetheless, it has been demonstrated that patients with severe obesity do benefit from KT over lifelong dialysis.[145,146] Consideration for KT in these patients is becoming more common as data emerge which demonstrate safety and overall benefit of undergoing MS prior to or after KT. A review of data from the ACS National Surgical Quality Improvement Program (NSQIP) showed no difference in 30-day adverse outcomes between DD and non-DD patients undergoing MS.[147] SG has become the most common metabolic procedure performed in ESRD patients, in part because of the concern for renal oxalate deposition and malabsorption associated with gastric bypass.[148,149] In one of the largest series of patients undergoing KT after SG, Kim and colleagues analyzed the outcomes of 41 patients and found an average decrease of 9 BMI points prior to KT with a significant decrease in the number of antihypertensive medications and insulin dependence. Importantly, no patients experienced NODAT. Only 1 patient had delayed graft function, and only 1 had graft loss. Thirty-day readmission was seen in 27.3% and surgical complications were noted in 7.3%.[150] A retrospective cohort study of 43 patients who underwent MS before KT and 21 after KT found no significant difference in change in BMI 5 years following surgery between the 2 groups. Propensity score matching against controls who had received KT but not undergone MS showed a decrease in risk of allograft failure and mortality in the MS cohort with the most profound effect seen in those who had surgery prior to KT.[151]

NAFLD is present in 30% of adults in the United States, with 42% progressing to non-alcoholic steatohepatitis (NASH).[152,153] Of those, one third will develop cirrhosis.[154] NAFLD is rapidly becoming the most common indication for liver transplantation (LTX) and is projected to be the leading cause of end stage liver disease in 2025.[155] As a consequence, a substantial percentage of patients who have ESLD are also morbidly obese. Although there is no universal BMI cutoff for LTX, many centers have imposed their own BMI limits which has subjected candidates with morbid obesity to longer wait times to receive an organ.[156] Older data have shown increased morbidity and mortality following bariatric surgery in patients with cirrhosis,[157,158] while more recent studies are emerging that demonstrates not only the relative safety of LTX in the morbidly obese, but the improved outcomes in those who receive BS. A recent meta-analysis included 8 studies that identified 187 patients who underwent MS prior to LTX. These patients experienced an average BMI reduction of 30.4%, from 45.7 to 31.8 kg/m^2, at 12 months. Eighty-two percent were successfully listed for transplant and 70% eventually received LTX. The graft survival at 1 year was 70% and the 30-day minor and major complication rates were 4% and 1%, respectively. Thirty-seven patients underwent a MS procedure at the time of LTX, with 0% 30-day mortality and 100% graft survival at 1 year. Finally, 64 patients had MS after LTX and had a 0% 30-day mortality rate with similar weight loss and resolution of comorbidities compared to matched controls who had undergone BS alone.[159] Although BS patients on chronic immunosuppression have been shown to have higher 30-day complication rates compared to non-immunosuppressed patients, this was noted to be most significant in anastomotic cases.[160] The largest retrospective case-control study of laparoscopic SG patients after LTX compared to matched controls who had not undergone LTX showed a longer hospital length of stay in the post-LTX group (1.5 vs 3.1 days) but no difference in conversion to open procedure, change in BMI, resolution of comorbidities, 30-day complications, or mortality.[161]

Heart failure has the strictest weight criteria for organ transplantation. This is due to higher graft failure seen in recipients with a BMI >35 kg/m^2 caused by an increase in cardiac demand in these patients.[162] Accordingly, the International Society for Heart Lung Transplantation published recommendations in 2016 to establish a BMI threshold for consideration in listing patients for cardiac transplantation to be <35 kg/m^2.[163] Because of this strict BMI criteria, most heart transplant recipients are not candidates for MS. Instead, MS may be needed in order to achieve the necessary weight loss before consideration of transplant. This is balanced against the finding that patients with heart failure are at increased risk of perioperative complications following bariatric surgery. One study demonstrated a higher 30-day mortality rate (odds ratio, 2.63) in patients with heart failure undergoing gastric bypass.[164]

Left ventricular assist devices (LVADs) are used as a bridge to cardiac transplant. Since there are no BMI cutoffs for LVAD placement, many obese patients awaiting cardiac transplantation may have undergone LVAD implantation prior to consideration for BS. Although the need for systemic anticoagulation with these devices increases bleeding risk, data from smaller case series have shown that MS can be accomplished safely with acceptable complication rates and significant weight loss that facilitates patients meeting criteria for cardiac transplantation. One study followed 5 patients with an LVAD who underwent BS as a bridge to transplant with 3 RYGB and 2 SG cases. At 12 months, 4 patients had lost sufficient weight to be transplanted and 1 patient was only 6 months out from MS and was not yet eligible for transplantation.[165] Another study reviewed 11 patients with LVADs who underwent SG. Four patients received a cardiac transplant with another 3 successfully achieving a BMI <35 kg/m^2 and waiting for transplant.[166] Yang and colleagues published a larger series of 21 patients with advanced heart failure in which 18 underwent gastric banding, 2 SG, and 1 BPD. At 12 months, 1 patient had received a heart transplant and 2 others were taken off the list due to significant improvement in cardiac function. The average BMI at the time of operation was 46.2 kg/m^2 and average weight loss was 26.0 kg.[167] Although the type of BS performed and resulting weight loss may have a strong impact on the number of patients who ultimately are transplanted, there is also evidence that weight loss in and of itself has significant effects on cardiac remodeling and improvement in ventricular systolic function.[168]

Although once considered to be a contraindication, patients with end stage organ disease are becoming increasingly recognized as a high-risk group that may substantially benefit from MS. However, larger prospective cohort studies are needed to better assess perioperative and long-term outcomes.

Can metabolic surgery be used for prophylaxis?

-Henry Buchwald, MD, PhD

Ten of the prior sections on applications of MS involve the prophylaxis of the onset of a disease and its secondary manifestations, the progression of a disease, and, ultimately, the fatal disease endpoint. MBS in the patient with obesity prevents, arrests, and may cure T2DM. In so doing, it is prophylactic with regard to the pathologic outcomes of T2DM: heart disease, stroke, high blood pressure, neuropathy, blindness, renal failure, lower extremity ulcerations, gastroparesis, Alzheimer's disease, and depression. Similar litanies of prevention after MBS are manifest for the sequelae of the metabolic diseases of hypertension, hyperlipidemia, heart disease, NAFLD, OSA, cancer, TBI, and CTE. Currently, modifications of MBS procedures to achieve one or more of the above disease benefits without, or with minimal, weight loss are being studied.

Serendipitously, MS devised for a particular disease may be prophylactic for another. For example, perirenal nerve ablation for hypertension mitigates T2DM.[169] Cervical vagal nerve stimulation by an implanted pacing mechanism intended to induce weight loss actually resolves refractory depression.[4] These neuro- or neurohormonal metabolic pathways influencing metabolic diseases are independent of surgery on the gastrointestinal tract, which has traditionally been associated with MS.

Prophylactic surgery, per se, has long been practiced; total or subtotal colectomy for chronic ulcerative colitis and familial polyposis to prevent colorectal cancer are established procedures. More recently, bilateral prophylactic mastectomies have been advocated for women with inherited autosomal dominant BRCA1 and BRCA2 genes. However, this surgery is directed toward the receptor end organs and is therefore not metabolic according to our definition of MS.

However, metabolic extension of the prophylactic concept of disease prevention, even to the concept of MS for a genetic alteration in a preceding generation is being practiced and may foretell future advocacy. Marceau and colleagues, in Montreal, studied the expression of genes for obesity and T2DM in women before and after MBS, as well as in their offspring.[170] The children born while the mothers were morbidly obese, as preteens were, or were becoming, obese and displayed signature markers for T2DM. Children, though, with the same fathers, born after the mothers had undergone MBS were not afflicted by obesity and T2DM. Genetic profiling documented genes for obesity and T2DM in all offspring, but failure of clinical gene expression occurred if conception was post MBS.

Ileal resection in infancy prevented adult hypercholesterolemia, and partial ileal bypass in patients with hypercholesterolemia who had sustained a prior myocardial infarction not only arrested and reversed the manifestations of atherosclerotic cardiovascular disease but prolonged life expectancy and, therefore, was prophylactic with regard to the progression of atherosclerosis outcomes. Furthermore, in examination of the POSCH database, the partial ileal bypass operation proved to be preventative, thus prophylactic, for the onset of T2DM later in life.

All of these partial ileal bypass benefits were achieved by an operation of less than 1 hour that can be performed as an outpatient procedure via a small (eg, appendectomy) incision or laparoscopically. Advocacy of partial ileal bypass for an entire population seems unreasonable. Encouraging partial ileal bypass early in life for children born with familial hypercholesterolemia and, possibly, for children with a strong genetic inclination for hypercholesterolemia, atherosclerosis, and early death, determined by buccal smear genetic analysis, is somewhat less fantastic.

MS is in the evolution of recognition. We are seeing the ice mountain above the surface of the iceberg but have yet to appreciate the other 90% that is integral to the concept. Eighty percent to 90% of all diseases are metabolic in origin or have a metabolic cofactor. Therefore, over time, the MS concept and the practice of MS will come to the forefront. The acceptance of MS reality will progress from an appreciation of its history to clinical therapeutic practice, and, finally, to prophylactic utilization.

What is the future of metabolic surgery?

-Scott A. Shikora, MD

Although the term "metabolic surgery" was first reported in 1978, it was not well recognized until more recently. Early BS was more focused on weight loss than the metabolic benefits of surgery such as the remission of T2DM and other comorbid conditions. However, over time, it was becoming increasingly clear that bariatric operations were very effective for treating the comorbid conditions and therefore BS was in fact, MS. The tremendous increase in the acceptance and use of BS made the term "metabolic surgery" more commonplace. Additionally, there has been growing interest for discovering the mechanisms by which bariatric operative procedures are metabolic. For example, is it the stimulation of the release of glucagon-like-peptide-1 (GLP-1) in the ileum after gastric bypass that is the etiology of the postoperative control of T2DM[171]?

One can imagine several pathways for MS to travel in the future. First, we can see the development and introduction of newer endoscopic and surgical procedures. These procedures would achieve the same metabolic effects of the current bariatric operations but might be less complex, safer, and/or more effective. Currently, there are several such procedures under investigation, both laparoscopic and endoscopic, including one anastomosis gastric bypass or duodenal switch, sleeve gastrectomy with transit bipartition, and the endoscopic gastroplasty. MS can be considered for treating comorbid conditions such as T2DM in patients with normal weight instead of reserving it for patients with severe obesity.

In addition to creating/upgrading procedures, we can anticipate that the physiologic actions of the bariatric procedures will be elucidated, enabling researchers to develop medications that mimic the actions of the operations without the risks. For example, the antidiabetic medication exenatide is a GLP-1receptor agonist. It is currently used to treat T2DM, but it also may achieve weight loss. Although it does not copy the restrictive characteristics of bariatric procedures, it does seem to elicit similar hormonal effects.

Lastly, one can anticipate that the success of MS for the treatment of the obesity-associated health conditions may attract researchers to target other conditions not associated with severe obesity. Currently, splenectomy is performed for the treatment of ITP, portal diversion is used for the treatment of glycogen storage diseases, and thalamic ablation is used to treat the tremors of Parkinson's disease. Like bariatric surgical procedures, these procedures qualify as metabolic. It is very likely that this is just the tip of the iceberg. Now that MS is established, it is sure to expand into other organ systems and other diseases.

Conclusions

Although the term "metabolic surgery" has been around over 30 years, it had little acceptance until the tremendous explosion in the popularity of BS. Bariatric operations are the quintessential examples of metabolic procedures and it was not long before clinicians saw the results bariatric surgeons had known for years. Since that time, MS has become widespread. This monograph described the adverse effects of severe obesity on several conditions such as heart disease, cancer, and hypertension and the beneficial effect of metabolic operations on these conditions.

In the future, one can anticipate an even greater role of MS, developing new and better procedures and addressing conditions currently not considered metabolic in nature.

References

1. Buchwald H, Varco RL, eds. *Metabolic surgery*. New York: Grune and Stratton, Publishers; 1978.
2. Buchwald H, Fobi MAL, Herron D, Brethauer S. Definition and history of metabolic surgery. *Am Coll Surg Bull*. 2019;104(2):44–52.
3. Mayberg HS, Lozano AM, Voon V, et al. Deep brain stimulation for treatment-resistant depression. *Neuron*. 2005;24(5):651–660.
4. Yuan W, Williams BN. Long-term vagus nerve stimulation for severe refractory depression: a case study with a six-year follow-up. *J* Neuropsych Clin Neurosci. 2012;24(4):E50–E51.
5. American College of Surgeons Bulletins December 2018 through June 2019. Bulletin.facs.org.
6. Blackstone R.P. The history of the American Society for Metabolic and Bariatric Surgery. In: The ASMBS Textbook of Bariatric Surgery, Vol 1. Nguyen N.T., Blackstone R.P., Morton J.M., Ponce J., Rosenthal R. (Eds), Springer-Verlag, New York, Pg. 47-59.
7. WHO (2018) – Fact sheet – Obesity and overweight. Updated February 2018. Available at: www.ourworldindata.org
8. Ogden CL, Carroll MD, Flegal KM. The prevalence of obesity in the United States. *JAMA*. 2014;312(2):189–190.
9. Kremen A, Linner J, Nelson C. An experimental evaluation of the nutritional importance of proximal and distal small intestine. *Ann Surg*. 1954;140:439–444.
10. Payne J, DeWind L, Commons R. Metabolic observations in patients with jejunocolic shunts. *Am J Surg*. 1963;106:273–289.
11. Mason EE, Ito C. Gastric bypass in obesity. *Surg Clin North Am*. 1967;47:1345–1352.
12. Alden JF. Gastric and jejunoileal bypass: A comparison in the treatment of morbid obesity. *Arch Surg*. 1977;112(7):799–806.
13. Griffen WO, Young VL, Stevenson CC. A prospective comparison of gastric and jejunoileal bypass operation for morbid obesity. *Ann Surg*. 1977;186(4):500–509.
14. Pories WJ, MacDonald Jr KG, Morgan EJ, et al. Surgical treatment of obesity and its effect on diabetes: 10-y follow-up. *Am J of Clin Nutr*. 1992;55(2):582S–585S.
15. Laws HL, Piantadosi S. Superior gastric reduction procedure for morbid obesity: a prospective, randomized trial. *Ann Surg*. 1981;193(3):334–340.
16. Mason EE. Vertical banded gastroplasty for obesity. *Arch Surg*. 1982;117:701–706.
17. Scopinaro N, Gianetta E, Civalleri D, et al. Bilio-pancreatic by-pass for obesity: II. Initial experience in man. *Br J Surg*. 1979;66:619–620.
18. Marceau P, Biron S, Bourque RA, et al. Biliopancreatic diversion with a new type of gastrectomy. *Obes Surg*. 1993;3(1):29–35.
19. Hess DS, Hess DW. Biliopancreatic diversion with a duodenal switch. *Obes Surg*. 1998;8:267–282.
20. Regan JP, Inabnet WB, Gagner M, Pomp A. Early experience with two-stage laparoscopic Roux-en-Y gastric bypass asan alternative in the super-super obese patient. *Obes Surg*. 2003;13(6):861–864.
21. Gagner M, Deitel M, Kalberer TL, Erickson AL, Crosby RD. The Second International Consensus Summit for Sleeve Gastrectomy, March 19–21, 2009. *Surg Obes Relat Dis*. 2009;5(4):476–485.
22. Doležalová-Kormanová K, Buchwald JN, Skochova D, et al. Five-year outcomes: Laparoscopic greater curvature plication for treatment of morbid obesity. *Obes Surg*. 2017;27(11):2818–2828.
23. Buchwald H, Avidor Y, Braunwald E, et al. Bariatric Surgery: A systematic review and meta-analysis. *JAMA*. 2004;292(14):1724.
24. Buchwald H, Estok R, Fahrbach K, et al. Weight and type 2 diabetes after bariatric surgery: systematic review and meta-analysis. *Am J Med*. 2009;122(3):248–256 e5.
25. Sjostrom L, Narbro K, Sjostrom CD, et al. Effects of bariatric surgery on mortality in Swedish obese subjects. *N Engl J Med*. 2007;357(8):741–752.
26. Zuegel NP, Lang RA, Huttl TP, et al. Complications and outcomes after laparoscopic bariatric surgery: LAGB versus LRYGB. *Langenbecks Arch Surg*. 2012;397(8):1235–1241.
27. Decker GA, Swain JM, Crowell MD, Scolapio JS. Gastrointestinal and nutritional complications after bariatric surgery. *Am J Gastroenterol*. 2007;102(11):2571–2580.
28. Yang W, Wang C, Shikora S, Kow L. Recommendations for metabolic and bariatric surgery during the COVID-29 Pandemic from IFSO. *Obes Surg*. 2020;30(6):2071–2073.
29. Parikh RM, Mohan V. Changing definitions of metabolic syndrome. *Indian J Endocrinol Metab*. 2012;16(1):7–12.
30. Expert panel on detection, evaluation, and treatment of high blood cholesterol in adults. *JAMA*. 2001;285(19):2486–2497.
31. Einhorn D. American College of Endocrinology position statement on the insulin resistance syndrome. *Endocr Pract*. 2003;9(Supplement 2):5–21.
32. Pories WJ, MacDonald Jr KG, Flicinger EG, et al. Is type II diabetes mellitus (NIDDM) a surgical disease? *Ann Surg*. 1992;215(6):633–642.
33. Pories WJ, Swanson MS, MacDonald KG, et al. Who would have thought it? An operation proves to be the most effective therapy for adult-onset diabetes mellitus. *Ann Surg*. 1995;222(3):339–350.
34. Buchwald H, Estok R, Fahrbach, et al. Weight and type 2 diabetes after bariatric surgery: systematic review and meta-analysis. *Am J Med*. 2009;122(3):248–256 e5.
35. Dixon JB, O'Brien PE, Playfair J, et al. Adjustable gastric banding and conventional therapy for type 2 diabetes: a randomized controlled trial. *JAMA*. 2008;299(3):316–323.

36. Mingrone G, Panunzi S, De Gaetano A, et al. Bariatric surgery versus conventional medical therapy for type 2 diabetes. *N Engl J Med*. 2012;366(17):1577–1585.
37. Schauer PR, Bhatt DL, Kirwan JP, et al. Bariatric surgery versus intensive medical therapy for diabetes—5-year outcomes. *N Engl J Med*. 2017;376(7):641–651.
38. Khorgami Z, Shoar S, Saber AA, et al. Outcomes of bariatric surgery versus medical management for type 2 diabetes mellitus: a meta-analysis of randomized controlled trials. *Obes Surg*. 2019;29(3):964–974.
39. Aminian A. Bariatric procedure selection in patients with type 2 diabetes: choice between Roux-en-Y gastric bypass or sleeve gastrectomy. *Surg Obes Relat Dis*. 2020;16(2):332–339.
40. Sjostrom L, Lindroos A-K, Peltonen M, et al. Lifestyle, diabetes, and cardiovascular risk factors 10 years after bariatric surgery. *N Engl J Med*. 2004;351:2683–2693.
41. Rubino F, Forgione A, Cummings DE, et al. The mechanism of diabetes control after gastrointestinal bypass surgery reveals a role of the proximal small intestine in the pathophysiology of type 2 diabetes. *AnnSurg*. 2006;244(5):41–49.
42. Chambers AP, Smith EP, Begg DP, et al. Regulation of gastric emptying rate and its role in nutrient-induced GLP-1 secretion in rats after vertical sleeve gastrectomy. *Am J Physiol Endocrinol Metab*. 2014;306(4):E424–E432.
43. Batterham RL, Cummings DE. Mechanisms of diabetes improvement following bariatric/metabolic surgery. *Diabetic Care*. 2016;39(6):893–901.
44. Noureddin M, Vipani A, Bresee C, et al. NASH leading cause of liver transplant in women: updated analysis of indications for liver transplant and ethnic and gender variances. *Am J Gastroenterol*. 2018;113(11):1649–1659.
45. Bedogni G, Miglioli L, Masutti F, et al. Prevalence of and risk factors for nonalcoholic fatty liver disease: the Dionysos nutrition and liver study. *Hepatology*. 2005;42(1):44–52.
46. Suzuki A, Diehl AM. Nonalcoholic steatohepatitis. *Annu Rev Med*. 2017;68:85–98.
47. Donnelly KL, Smith CI, Schwarzenberg SJ, et al. Sources of fatty acids stored in liver and secreted via lipoproteins in patients with nonalcoholic fatty liver disease. *J Clin Invest*. 2005;115(5):1343–1351.
48. McCarty YR, Echouffo-Tcheugui JB, Lange A, et al. Impact of bariatric surgery on outcomes of patients with nonalcoholic fatty liver disease: a nationwide inpatient sample analysis, 2004–2012. *Surg Obes Relat Dis*. 2018;14(1):74–80.
49. Wirth KM, Sheka AC, Kizy S, et al. Bariatric surgery is associated with decreased progression of nonalcoholic fatty liver disease to cirrhosis: a retrospective cohort analysis. *Ann Surg*. 2020;272(1):32–39.
50. Mummadi RR, Kasturi KS, Chennareddgari S, et al. Effect of bariatric surgery on nonalcoholic fatty liver disease: systematic review and meta-analysis. *Clin Gastroenterol and Hepatol*. 2008;6(12):1396–1402.
51. Subichin M, Firstenberg MS. Liver disease in the morbidly obese: a review of 1000 consecutive patients undergoing weight loss surgery. *Surg Obes Relat Dis*. 2015;11(1):137–141.
52. Courcoulas A.P., Wolfe B.M., LABS Project. In: The ASMBS Textbook of Bariatric Surgery, Vol 1. Nguyen N.T., Blackstone R.P., Morton J.M., Ponce J., Rosenthal R. (Eds), Springer-Verlag, New York, Pg. 47-59.
53. Ravesloot MJ, van Maanen JP, Hilgevoord AA, van Wagensveld BA, de Vries N. Obstructive sleep apnea is underrecognized and underdiagnosed in patients undergoing bariatric surgery. *Eur Arch Otorhinolaryngol*. 2012;269:1865–1871.
54. de Raaff CA, Pierik AS, Coblijn UK, de Vries N, Bonjer HJ, van Wagensveld BA. Value of routine polysomnography in bariatric surgery. *Surg Endosc*. 2017;31:245–248.
55. Fonseca MI, Pereira T, Caseiro P. Death and disability in patients with sleep apnea—a meta-analysis. *Arg Bras Cardiol*. 2015;104:58–66.
56. Junnum P, Tonnesen P, Ibsen R, kjellberg J. All-cause mortality from obstructive sleep apnea in male and female patients with and without continuous positive airway pressure treatment: a registry study 10 years of follow-up. *Nat Sci Sleep*. 2015;7:43–50.
57. Marshall NS, Wong KK, Liu PY, Cullen SR, Knuiman MW, Grunstein RR. Sleep apnea as an independent risk factor for all-cause mortality: the Busselton Health Study. *Sleep*. 2008;31:1079–1085.
58. Giles T.L., Lasserson T.J., Smith B.H., White J., Wright J., Cates C.J. Continuous positive airways pressure for obstructive sleep apnoea in adults. *Cochrane Database Syst Rev*206;19:CD001106.
59. Wolkove N, Baltzan M, Kamel H, Dabrusin R, Palayew M. Long-term compliance with continuous positive airway pressure in patients with obstructive sleep apnea. *Can Respir J*.. 2008;15:365–369.
60. Rauscher H, Formanek D, Popp W, Zwick H. Self-reported vs measured compliance with Nasal CPAP for obstructive sleep apnea. *Chest*. 1993;103:1675–1680.
61. Holty JE, Guilleminault C. Surgical options for the treatment of obstructive sleep apnea. *Med Clin North Am*. 2010;94:479–515.
62. Khan A, Ramar K, Maddiraala S, Friedman O, Pallanch JF, Olson EJ. Uvulopalatopharyngoplasty in the management of obstructive sleep apnea. The mayo clinic experience. *Mayo Clin Proc*. 2009;84:795–800.
63. Peppard PE, Young T, Palta M, Dempsey J, Skatrud J. Longitudinal study of moderate weight change and sleep-disordered breathing. *JAMA*. 2000;284:3015–3021.
64. Suratt PM, McTier RF, Findey LJ, Pohl SL, Wilhoit SC. Changes in breathing and the pharynx after weight loss in obstructive sleep apnea. *Chest*. 1987;92:631–637.
65. Greenburg DL, Lettieri CJ, Eliasson AH. Effects of surgical weight loss on measures of obstructive sleep apnea: A meta-analysis. *Am J Med*. 2009;122:535–542.
66. Charuzi I, Lavie P, Peiser J, Peled R. Bariatric surgery in morbidly obese sleep-apnea patients: short- and long-term follow-up. *Am J Clin Nutr*. 1992;55(2 Suppl):594S–596S.
67. Fritscher LG, Mottin CC, Canani S, Chatkin JM. Obesity and obstructive sleep apnea-hypopnea syndrome: the impact of bariatric surgery. *Obes Surg*. 2007;17:95–99.
68. Lettieri CJ, Eliasson AH, Greenburg DL. Persistence of obstructive sleep apnea after surgical weight loss. *J Clin Sleep Med*. 2008;4:333–338.
69. ASMBS Clinical Issues Committee. Peri-operative management of obstructive sleep apnea. *Surg Obes Relat Dis*. 2012;8:e27–e32.

70. Calle EE. Obesity and cancer. *BMJ*. 2007;335:1107–1108.
71. Reneham AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body mass index and incidence of cancer: a systemic review and meta-analysis of prospective observational studies. *Lancet*. 2008;371:569–578.
72. Reeves GK, Pirie K, Beral V, Green J, Spencer E, Bull D. Cancer incidence and mortality in relation to body mass index in the Million Women Study: cohort study. *BMJ*. 2007;335:1134.
73. Schauer DP, Feigelson HS, Koebnick C, et al. Bariatric Surgery and the risk of cancer in a large multisite cohort. *Ann Surg*. 2019;269:95–101.
74. Lauby-Secretan B, Vilahur N, Bianchini F, Guha N, Straif K. International Agency for Research on Cancer Handbook Working Group. Body fatness and cancer. *N Engl J Med*. 2016;25:794–798.
75. Steele CB, Thomas CC, Henley SJ, et al. Vital signs: trends in incidence of cancers associated with overweight and obesity - United States, 2005-2014. *MMWR*. 2017;66:1052–1058.
76. Schauer DP, Feigelson HS, Koebnick C, et al. Association between weight loss and the risk of cancer after bariatric surgery. *Obesity*. 2017;25(Suppl 2):S52–S57.
77. Adams TD, Stroup AM, Gress RW, et al. Cancer incidence and mortality after gastric bypass surgery. *Obesity*. 2009;17:796–802.
78. Trentham-Dietz A, Nichols HB, Hampton JM, Newcomb PA. Weight change and risk of endometrial cancer. *Int J Epidemiol*. 2006;35:151–158.
79. Winder AA, Kularatna M, MacCormick AD. Does bariatric surgery affect the incidence of endometrial development? A systematic Review. *Obes Surg*. 2018;28:1433–1440.
80. Winder AA, Kularatna M, MacCormick AD. Does bariatric surgery affect the incidence of breast cancer development? A systematic Review. *Obes Surg*. 2017;27:3014–3020.
81. Sjöström L, Narbro K, Sjöström CD, et al. Swedish Obese Subjects Study. Effects of bariatric surgery on mortality in Swedish obese subjects. *N Engl J Med*. 2007;357:741–752.
82. Abe R, Kumagai N, Kimura M, et al. Biological characteristics of breast-cancer in obesity. *Tokoku* J Exp Med. 1976;120:351–359.
83. Lee K, Kruper L, Dieli-Conwright CM, et al. The impact of obesity on breast cancer diagnosis and treatment. *Curr Oncol Rep*. 2019;21:41–47.
84. Câmara NOS, Iseki K, Kramer H, Liu Z-H, Sharma K. Kidney disease and obesity: epidemiology, mechanisms and treatment. *Nat Rev Nephrol*. 2017;13:181–190.
85. Hainer V, Aldhoon-Hainerova I. Obesity paradox does exist. *Diabetes Care*. 2013;36:S276–S281.
86. Hall J, Juncos L, Wang Z, Hall M, Carmo Jdo, Silva Ada. Obesity, hypertension, and chronic kidney disease. *Int J Nephrol Renovascular Dis*. 2014;7:75–88.
87. Hsu C, McCulloch CE, Iribarren C, Darbinian J, Go AS. Body Mass Index and Risk for End-Stage Renal Disease. *Ann Intern Med*. 2006;144:21–28.
88. Segev DL, Simpkins CE, Thompson RE, Locke JE, Warren DS, Montgomery RA. Obesity Impacts Access to Kidney Transplantation. *J Am Soc Nephrol*. 2008;19:349–355.
89. Diwan TS, Lee TC, Nagai, et al. Obesity, transplantation, and bariatric surgery: An evolving solution for a growing epidemic. *Am J Transplant*. 2020;20:2143–2155.
90. Imam TH, Fischer H, Jing B, et al. Estimated GFR Before and After Bariatric Surgery in CKD. *Am J Kidney Dis*. 2017;69:380–388.
91. Liakopoulos V, Franzén S, Svensson A-M, et al. Renal and cardiovascular outcomes after weight loss from gastric bypass surgery in type 2 diabetes: cardiorenal risk reductions exceed atherosclerotic benefits. *Diabetes Care*. 2020;43:1276–1284.
92. Agrawal V, Navaneethan SD. Bariatric surgery for obesity-associated decline in kidney function: filling the knowledge gap? *Kidney Int*. 2016;90:28–30.
93. Navaneethan SD, Kelly KR, Sabbagh F, Schauer PR, Kirwan JP, Kashyap SR. Urinary Albumin Excretion, HMW Adiponectin, and Insulin Sensitivity in Type 2 Diabetic Patients Undergoing Bariatric Surgery. *Obes Surg*. 2010;20:308–315.
94. Nehus EJ, Khoury JC, Inge TH, et al. Kidney outcomes three years after bariatric surgery in severely obese adolescents. *Kidney Int*. 2017;91:451–458.
95. Choudhury RA, Yoeli D, Moore HB, et al. Reverse epidemiology and the obesity paradox for patients with chronic kidney disease: a Markov decision model. *Surg Obes Relat Dis*. 2020;16:948–954.
96. Choudhury RA, Hoeltzel G, Prins K, et al. Sleeve gastrectomy compared with gastric bypass for morbidly obese patients with end stage renal disease: a decision analysis. *J Gastrointest Surg*. 2020;24:756–763.
97. Sheetz KH, Gerhardinger L, Dimick JB, Waits SA. Bariatric surgery and long-term survival in patients with obesity and end-stage kidney disease. *JAMA Surgery*. 2020;155:1–8.
98. Sheetz KH, Woodside KJ, Shahinian VB, Dimick JB, Montgomery JR, Waits SA. Trends in bariatric surgery procedures among patients with ESKD in the United States. *Clin J Am Soc Nephro*. 2019;14:1193–1199.
99. Kim Y, Jung AD, Dhar VK, et al. Laparoscopic sleeve gastrectomy improves renal transplant candidacy and post-transplant outcomes in morbidly obese patients. *Am J Transplant*. 2018;18:410–416.
100. Kassam A, Mirza A, Kim Y, et al. Long-term outcomes in patients with obesity and renal disease after sleeve gastrectomy. *Am J Transplant*. 2020;20:422–429.
101. Hall ME, do Carmo JM, da Silva AA, Juncos LA, Wang Z, Hall JE. Obesity, hypertension, and chronic kidney disease. *Int J Nephrol Renovascular Dis*. 2014;7:75–88.
102. Jones DW, Miller ME, Wofford MR, et al. The effect of weight loss intervention on antihypertensive medication requirements in the hypertension optimal treatment (HOT) study. *Am J Hypertens*. 1999;12:1175–1180.
103. Stevens VJ, Obarzanek E, Cook NR, et al. Long-term weight loss and changes in blood pressure: results of the trials of hypertension prevention, phase II. Ann Intern *Med*. 2001;134:1–11.
104. Ikramuddin S, Korner J, Lee W-J, et al. Roux-en-Y gastric bypass vs intensive medical management for the control

of type 2 diabetes, hypertension, and hyperlipidemia: the diabetes surgery study randomized clinical trial. *JAMA*. 2013;309:2240–2249.
105. Ikramuddin S, Korner J, Lee W-J, et al. Lifestyle intervention and medical management with vs without Roux-en-Y gastric bypass and control of Hemoglobin A 1c, LDL cholesterol, and systolic blood pressure at 5 years in the diabetes surgery study. *JAMA*. 2018;319:266–278.
106. Schiavon CA, Bersch-Ferreira AC, et al. Effects of bariatric surgery in obese patients with hypertension. *Circulation*. 2018;137:1132–1142.
107. Schiavon CA, Bhatt DL, Ikeoka D, et al. Three-year outcomes of bariatric surgery in patients with obesity and hypertension: a randomized clinical trial. *Ann Intern Med*. 2020;173(9):685–693.
108. Sarkhosh K, Birch DW, Shi X, Gill RS, Karmali S. The impact of sleeve gastrectomy on hypertension: a systematic review. *Obes Surg*. 2012;22:832–837.
109. Salminen P, Helmiö M, Ovaska J, et al. Effect of Laparoscopic Sleeve Gastrectomy vs Laparoscopic Roux-en-Y Gastric Bypass on Weight Loss at 5 Years Among Patients With Morbid Obesity. *JAMA*. 2018;319:241 –14.
110. Nudotor RD, Canner JK, Prokopowicz GP, Haut ER, Steele KE. Comparing remission and recurrence of hypertension after bariatric surgery: vertical sleeve gastrectomy versus Roux-en-Y gastric bypass. *Surg Obes Relay Dis.*. 2020;Oct 1 S1550-7289(20)30565-7Online. doi:10.1016/j.soard.2020.09.035.
111. Kenchaiah S, Evans JC, Levy D, Wilson PWF, Benjamin EJ, Larson MG, Kannel WB, Vasan RS. Obesity and the risk of heart failure. *N Engl J Med*. 2002;347:305–313.
112. Khan SS, Ning H, Wilkins JT, et al. Association of body mass index with lifetime risk of cardiovascular disease and compression of morbidity. *JAMA Cardiol*. 2018;3:280–287.
113. The Emerging Risk Factors CollaborationSeparate and combined associations of body-mass index and abdominal adiposity with cardiovascular disease: collaborative analysis if 58 prospective studies. *Lancet*. 2011;377:1085–1095.
114. Yusuf S, Hawken S, Ounpuu S, et al. Obesity and the risk of myocardial infarction in 27000 participants from 52 countries: a case-control study. *Lancet*. 2005;366:1640–1649.
115. Calle EE, Thun MJ, Petrelli JM, Rodriguez, Heath Jr CW. Body-mass index and mortality in a prospective cohort of U.S. adults. *New Engl J Med*. 1999;341:1097–1105.
116. Wang TJ, Parise H, Levy D, et al. Obesity and the Risk of new-onset atrial fibrillation. *JAMA*. 2004;292:2471–2477.
117. Owan T, Avelar E, Morley K, et al. Favorable changes in cardiac geometry and function following gastric bypass surgery. *J Am Coll Cardiol*. 2011;57:732–739.
118. Stevens J, Cai J, Evenson KR, Thomas R. Fitness and fatness as predictors of mortality from all causes and from cardiovascular disease in men and women in the lipid research clinics study. *Am* J Epidemiol. 2002;156:832–841.
119. Henriksson H, Henriksson P, Tyelius P, et al. Cardiorespiratory fitness, muscular strength, and obesity in adolescence and later chronic disability due to cardiovascular disease: a cohort study of 1 million men. *Eur Heart J*. 2020;41:1503–1510.
120. Buchwald H. Lowering of cholesterol absorption and blood levels by ileal exclusion: Experimental basis and preliminary clinical report. *Circulation*. 1964;29(5):713–720.
121. Moore RB, Frantz Jr ID, Buchwald H. Changes in cholesterol pool size, turnover rate, and fecal bile acid and sterol excretion after partial ileal bypass in hypercholesterolemic patients. *Surgery*. 1969;65(1):98–108.
122. Buchwald H, Varco RL, Matts JP, et al. Effect of partial ileal bypass surgery on mortality and morbidity from coronary heart disease in patients with hypercholesterolemia. Report of the Program on the Surgical Control of the Hyperlipidemias (POSCH). *N Engl J Med*. 1990;323(14):946–955.
123. Campos CT, Buchwald H. Lipid lowering and regression of atherosclerosis. partial ileal bypass surgery. *Controversies Card*. 1993;4:9–12.
124. Buchwald H, Rudser KD, Williams SE, Michalek VN, Vagasky J, Connett JE. Overall mortality, incremental life expectancy, and cause of death at 25-years in the Program on the Surgical Control of the Hyperlipidemias (POSCH). *Ann Surg*. 2010;251(6):1034–1040.
125. Buchwald H, Oien DM, Schieber DJ, Bantle JP, Connett JE. Partial ileal bypass affords protection from onset of type 2 diabetes. *Surg Obes Relat Dis*. 2017;13(1):45–51.
126. McGlennon TW, Buchwald JN, Pories WJ, et al. Bypassing TBI: Metabolic surgery and the link between obesity and traumatic brain injury. *Obes Surg*. 2020;30(12):4704–4714.
127. Omala BI, DeKsky ST, Minster RL, Kamboh MI, Hamilton RL, Wecht CH. Chronic traumatic encephalopathy in a National Football league player. *Neurosurgery*. 2005;57(1):128–134.
128. Mez J, Daneshvar DH, Kiernan PT, et al. Clinicopathological evaluation of chronic traumatic encephalopathy in players of American football. *JAMA*. 2017;318(4):360–370.
129. McKee AC, Cantu RC, Nowinski CI, et al. Chronic traumatic encephalopathy in athletes: progressive tauopathy following repetitive head injury. *J Neuropathol Exp Neurol*. 2009;68(7):709–735.
130. Werhane ML, Evangelista ND, Clark AL, et al. Pathological vascular and inflammatory biomarkers of acute- and chronic-phase traumatic brain injury. *Concussion*. 2017;2(1):CNC30.
131. Alosco ML, Stein TD, Tripodis Y, et al. Association of white matter rarefaction, arteriosclerosis, and tau with dementia in chronic traumatic encephalopathy. *JAMA Neurol*. 2019;76(11):1298–1308.
132. Churchill TW, Krishnan S, Weisskopf M, et al. Weight gain and health affliction among former National Football League players. *Am J Med*. 2018;131(12):1491–1498.
133. Wang C, Chan JS, Ren L, Yn JH. Obesity reduces cognitive and motor functions across the lifespan. *Neural Plast*. 2016;2016:2473081.
134. Enzinger C, Fazekas F, Matthews PM, et al. Risk factors for progression of brain atrophy in aging: six-year follow-up of normal subjects. *Neurology*. 2005;64(10):1704–1711.
135. Gunstad J, Paul RH, Cohen RA, Tate DF, Spitznagel MB, Gordon E. Elevated body mass index is association with executive dysfunction in otherwise healthy adults. *Compr Psychiatry*. 2007;48(1):57–61.
136. Castanon N, Lasselin J, Capuron L. Neuropsychiatric comorbidity in obesity: role of inflammatory processes. *Front Endocrinol*. 2014;5:74.

137. Marques EL, Halpern A, Correa Mancini M, et al. Changes in neuropsychological tests and brain metabolism after bariatric surgery. *J Clin Endocrinol Metab*. 2014;99(11):E2347–E2352.
138. Thiara G, Cigliobianco M, Muravsky A, et al. Evidence for neurocognitive improvement after bariatric surgery: a systemic review. *Psychosomatics*. 2017;58(3):217–227.
139. Alosco ML, Galioto R, Spitznagel MB, et al. Cognitive function after bariatric surgery: evidence for improvement 3 years after surgery. *Am J Surg*. 2014;207(6):870–876.
140. Montgomery JR, Ghaferi AA, Waits SA. Bariatric surgery among patients with end-stage kidney disease: improving access to transplantation. *Surg Obes Relat Dis*. 2020;16(1):14–16.
141. Massarweh NN, Clayton JL, Mangum CA, Florman SS, Slakey. High body mass index and short-and long-term renal allograft survival in adults. *Transplantation*. 2005;80(10):1430–1434.
142. Segev DL, Simpkins CE, Thompson RE, Locke JE, Warrne DS, Montgomery RA. Obesity impacts access to kidney transplantation. *J Am Soc of Nephrol*. 2008;19(2):349–355.
143. Mazzei M, Zhao H, Edwards MA. The impact of chronic kidney disease on bariatric perioperative outcome: a MB-SAQIP matched analysis. *Surg Obes Relat Dis*. 2019;15(12):2075–2086.
144. Jialin W, Yi Z, Weijie Y. Relationship between body mass index and mortality in hemodialysis patients: a meta–analysis. *Nephron Clin Pract*. 2012;121(3-4):c102–c111.
145. Pelletier SJ, Maraschio MA, Schaubel DE, et al. Survival benefit of kidney and liver transplantation for obese patients on the waiting list. *Clin Transpl*. 2003:77–88.
146. Marks WH, Florence LS, Chapman PH, Precht AF, Perkinson DT. Morbid obesity is not a contraindication to kidney transplantation. *Am J Surg*. 2004;187(5):635–638.
147. Andalib A, Aminian A, Khorgami Z, Navaneethan SD, Schauer PR, Brethauer. Safety analysis of primary bariatric surgery in patients on chronic dialysis. *Surg Endosc*. 2016;30(6):2583–2591 Mozer AB.
148. Pender 4th JR, Chapman WH, Sippey ME, Pories WJ, Spaniolas K. Bariatric surgery in patients with dialysis-dependent renal failure. *Obes Surg*. 2015;25(11):2088–2092.
149. Upala S, Jaruvongvanich V, Sanguankeo A. Risk of nephrolithiasis, hyperoxaluria, and calcium oxalate supersaturation increased after Roux-en-Y gastric bypass surgery: a systematic review and meta-analysis. *Surg Obes Relat Dis*. 2016;12(8):1513–1521.
150. Kim Y, Bailey AJ, Morris MC, et al. Kidney transplantation after sleeve gastrectomy in the morbidly obese candidate: results of a 2-year experience. *Surg Obes Relat Dis*. 2020;16(1):10–14.
151. Cohen JB, Lim MA, Tewksbury CM, et al. Bariatric surgery before and after kidney transplantation: long-term weight loss and allograft outcomes. *Surg Obes Relat Dis*. 2019;15(6):935–941.
152. Angulo P. Nonalcoholic fatty liver disease. *N Engl J Med*. 2002;346(16):1221–1231.
153. Agopian VG, Kaldas FM, Hong JC, et al. Liver transplantation for nonalcoholic steatohepatitis: the new epidemic. *Ann Surg*. 2012;256(4):624–633.
154. Suzuki A, Diehl AM. Nonalcoholic steatohepatitis. *Annu Rev Med*. 2017;68:85–98.
155. Wong RJ, Aguilar M, Cheung R, et al. Nonalcoholic steatohepatitis is the second leading etiology of liver disease among adults awaiting liver transplantation in the United States. *Gastroenterology*. 2015;148(3):547–555.
156. Segev DL, Thompson RE, Locke JE, et al. Prolonged waiting times for liver transplantation in obese patients. *Ann Surg*. 2008;248(5):863–870.
157. Mosko JD, Nguyen GC. Increased perioperative mortality following bariatric surgery among patients with cirrhosis. *Clin Gastroenterol Hepatol*. 2011;9(10):897–901.
158. Thuluvath PJ. *Morbid obesity with one or more other serious comorbidities should be a contraindication for liver transplantation*. Wiley Online Library; 2007.
159. Lee Y, Tian C, Lovrics O, et al. Bariatric surgery before, during, and after liver transplantation: a systematic review and meta-analysis. *Surg Obes Relat Dis*. 2020;16(9):1336–1347.
160. Hefler J, Dang J, Modasi A, Switzer N, Birch DW, Karmali S. Effects of chronic corticosteroid and immunosuppressant use in patients undergoing bariatric surgery. *Obes Surg*. 2019;29(10):3309–3331.
161. Tsamalaidze L, Stauffer JA, Arasi LC, et al. Laparoscopic sleeve gastrectomy for morbid obesity in patients after orthotopic liver transplant: a matched case-control study. *Obes Surg*. 2018;28(2):444–450.
162. Weiss ES, Allen JG, Russell SD, Shah AS, Conte JV. Impact of recipient body mass index on organ allocation and mortality in orthotopic heart transplantation. *J Heart Lung Transplant*. 2009;28(11):1150–1157.
163. Mehra MR, Canter CE, Hannan MM, et al. The 2016 International Society for Heart Lung Transplantation listing criteria for heart transplantation: a 10-year update. *J Heart Lung Transplant*. 2016;35(1):1–23.
164. Benotti P, Wood GC, Winegar DA, et al. Risk factors associated with mortality after Roux-en-Y gastric bypass surgery. *Ann Surg*. 2014;259(1):123–130.
165. Pullatt R, Crowley NM, Byrne KT, Axiotis D. Bariatric surgery as a bridge to cardiac transplantation in patients with LVAD. *Surg Obes Relat Dis*. 2018;14(11):S121–S122.
166. Hawkins RB, Go K, Raymond SL, Ayzengart A, Frieda J. Laparoscopic sleeve gastrectomy in patients with heart failure and left ventricular assist devices as a bridge to transplant. *Surg Obes Relat Dis*. 2018;14(9):1269–1273.
167. Yang TWW, Johari JY, Burtion JY, et al. Bariatric surgery in patients with severe heart failure. *Obes Surg*. 2020;30(8):2863–2869.
168. Kindel TL, Strande JL. Bariatric surgery as a treatment for heart failure: review of the literature and potential mechanisms. *Surg Obes Relat Dis*. 2018;14(1):117–122.
169. Mahfoud F, Schlaich M, Kindermann I, et al. Effect of renal sympathetic denervation on glucose metabolism in patients with resistant hypertension: a pilot study. *Circulation*. 2011;123(18):1940–1946.
170. Guénard F, Deshaies Y, Cianflone K, Kral JG, Marceau P, Vohl MC. Differential methylation in glucosoregulatory genes of offspring born before vs. after maternal gastrointestinal bypass surgery. *Proc Natl Acad Sci USA*. 2013;110(28):11439–11444.
171. Le Roux CW, Aylwin SJB, Batterham RL, et al. Gut hormone profiles following bariatric surgery favor an anorectic state, facilitate weight loss and improve metabolic parameters. *Ann Surg*. 2006;243(1):108–114.