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The Safety and Efficacy of Bariatric Surgery: The Longitudinal Assessment of Bariatric Surgery (LABS)

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Abstract

Background—Obesity is a leading health concern in the United States. Since traditional treatment approaches for weight loss are generally unsuccessful long-term [1], bariatric surgical procedures are increasingly being performed to treat extreme obesity. To facilitate research in this field, the National Institute of Diabetes and Digestive and Kidney Diseases responded to this knowledge gap by establishing the Longitudinal Assessment of Bariatric Surgery (LABS) consortium.

Methods—A competitive NIDDK grant process resulted in the creation of a group of investigators with expertise in bariatric surgery, internal medicine, endocrinology, behavioral science, outcomes research, epidemiology, biostatistics and other relevant fields who have worked closely to plan, develop, and conduct the LABS study. The LABS consortium protocol is a prospective, multi-center observational cohort study of consecutive patients undergoing bariatric surgery at six clinical centers. LABS includes an extensive database of information systematically collected pre-operatively, at surgery, and perioperatively during the 30 day post-operative period, and longer term.

Results—The LABS study is organized into three phases. LABS-1 includes all patients at least 18 years of age who undergo bariatric surgery by LABS-certified surgeons with the goal to evaluate the short-term **safety** of bariatric surgery. LABS-2, a subset of approximately 2400 LABS-1 patients, evaluates the relationship of patient and surgical characteristics to longer-term safety and **efficacy** of bariatric surgery. LABS-3 involves a subset of LABS-2 subjects who undergo detailed studies of **mechanisms** involved in weight change. The rationale, goals, and approach to study bariatric surgery are detailed in this report along with a description of the outcomes, measures, and hypotheses utilized in LABS-1 and -2.

Conclusions—The goal of the LABS consortium is to accelerate clinical research and understanding of extreme obesity and its complications by evaluating the risks and benefits of bariatric surgery. LABS investigators use standardized definitions, high fidelity data collection, and validated instruments to enhance the ability of clinicians to provide meaningful evidence-based recommendations for patient evaluation, selection for surgery, and follow-up care.

Keywords

Bariatric Surgery; Obesity

Introduction

Obesity is one of the leading health concerns in the United States (US). Traditional treatment approaches for weight loss such as diet, exercise, and medications generally achieve no more than a 5-15% reduction in body weight [2,3]. Furthermore, a majority of obese individuals who lose weight return to, or exceed, their baseline weight when followed over five years [1,4]. As a result, bariatric surgical procedures that restrict stomach size or lead to altered absorption of nutrients are increasingly being performed to treat extreme obesity. These procedures often result in significant and sustained weight loss [5] and can have a dramatic effect on co-morbid conditions associated with obesity [6]. However, it is not clear that short-term improvement in all co-morbid conditions is sustained over time [7]. Bariatric

procedures also have considerable short and long-term risks that must be balanced against these benefits.

The use of bariatric procedures has grown considerably over the last decade. In 1995, fewer than 20,000 bariatric operations were performed. In 2005, 180,000 bariatric procedures were performed, and in 2006, over 200,000 procedures are expected [8]. Factors contributing to such growth may include the prevalence of obesity, the increase in reports of surgical efficacy, the availability of less invasive procedures, and the media exposure of successful bariatric procedures [9]. Still, less than 1% of the 23 million morbidly obese patients in the United States undergo bariatric procedures. [9] One possible explanation for the disparity between potentially eligible patients and numbers of procedures performed is financial, i.e., patients may not be able to gain insurance coverage or have the ability to pay for a procedure out of pocket. Another potential reason is uncertainty regarding potential risks and benefits among both patients and referring physicians. This is particularly salient because during the years that bariatric procedures were being developed, they were associated with high complication rates, failure to lose weight, and a need for frequent re-operations.

In 1991, the National Institutes of Health held a Consensus Development Conference on Gastrointestinal Surgery for Severe Obesity [10] at which time several research questions related to bariatric surgery were posed that have not yet been answered, more than 15 years later. These include a thorough understanding of the safety and efficacy of bariatric surgery and mechanisms by which surgery leads to weight reduction and improvements in co-morbid conditions. This knowledge gap stems, in part, from the lack of standardized data collection methods, procedures, and outcomes assessments. A National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)-sponsored Working Group on Research in Bariatric Surgery , convened in May 2002, advised that a consortium of centers that perform bariatric surgical procedures be established to develop a database to collect information on clinically important predictors and outcomes that would benefit clinical research and understanding of bariatric surgery and its sequelae [11]

In response, a Request for Applications (RFA) was released by NIDDK in November 2002 to establish and maintain a Bariatric Surgery Research Consortium, comprised of clinical centers and a data coordinating center. The primary focus of this consortium was to support collaborative clinical, epidemiological, and behavioral research by focusing on the role of bariatric surgery in treating obesity and its complications. The competitive, peer review, process resulted in the selection of six Clinical Centers and one Data Coordinating Center (DCC). As a result, in September 2003, the NIDDK established the Longitudinal Assessment of Bariatric Surgery (LABS) consortium. Researchers in the LABS consortium have expertise in bariatric surgery and obesity as well as internal medicine, endocrinology, behavioral science, outcomes research, epidemiology, biostatistics and other relevant fields. These Clinical Center investigators have worked closely with a DCC in cooperation with NIDDK scientific staff to plan, develop, and conduct coordinated clinical, epidemiological, and behavioral research associated with bariatric procedures.

The six participating clinical centers are the University of Pittsburgh Medical Center (Pennsylvania), Columbia-Presbyterian and Weill-Cornell University Medical Centers comprising New York Presbyterian Hospital (New York), University Health Systems of Eastern North Carolina and East Carolina University (North Carolina), Neuropsychiatric Research Institute (North Dakota), Oregon Health and Science University and Legacy Good Samaritan Hospital, (Oregon) and Virginia Mason Hospital and the University of Washington (Washington). The DCC is located at the Graduate School of Public Health at the University of Pittsburgh. The LABS governing body, or Steering Committee, is

comprised of the six Clinical Center Principal Investigators, the DCC Principal Investigator, and the NIDDK Project Scientist.

This paper explains the rationale, goals, and approach that this consortium has formulated to comprehensively assess bariatric surgical procedures; by examining in-depth safety and efficacy, investigating clinically important predictors and outcomes of these procedures, and exploring mechanisms by which surgery leads to weight reduction and health improvements. In addition, the key outcome domains, hypotheses being tested, and research tools studied in LABS are elucidated.

The Longitudinal Assessment of Bariatric Surgery (LABS)

Rationale for Research Designs in Bariatric Surgery

The 1991 NIH Consensus Conference generated several important and unanswered questions. The LABS Steering Committee initially considered several potential study designs to address such questions and determined that, within the constraints of available time and resources, an observational study was the most efficient means to test a multitude of important hypotheses about bariatric procedures. Hence, LABS includes at its core, a multi-center, observational database including prospectively collected detailed patient and operative characteristics; short and longer-term clinical outcomes; and behavioral and health system outcomes. Because relatively little is known about the factors involved in adverse and favorable outcomes in bariatric surgery, a meticulously designed and implemented database that includes substantial data in a variety of content areas was considered necessary to test a multitude of hypotheses. Although randomized clinical trials provide higher order evidence of efficacy than do observational studies, the number of questions that can be addressed by a clinical trial is more limited.

In addition, the context of this decision to favor an observational study over a randomized controlled trial (RCT) was guided by the fact that research in the field of bariatric surgery has been associated with several challenges in the study of surgical versus non-surgical treatment for severe obesity; feasibility, lack of comparable outcomes, and ethical issues. Past RCTs have compared procedures (e.g., vertical banded gastroplasty versus gastric bypass [12]) or surgical techniques (e.g., laparoscopic versus open gastric bypass [13]). However, there are considerable ethical and compliance barriers to a RCT comparing operative and non-operative approaches to obesity treatment. In 1995, the Swedish Obesity Subjects study (SOS), the largest prospective study to date of bariatric surgery, was unable to obtain Institutional Review Board approval for a RCT of bariatric surgery versus medical care due to the known risks and unclear expected benefits of surgical therapy [14]. Randomizing patients who do not have access to bariatric surgery for financial reasons was also considered by the LABS Steering Committee. This option was ruled out as the research funds that would be required to pay for both the surgical and medical interventions were not available and the financial incentive of a potentially cost-free operation was judged to represent excessive coercion. Furthermore, in its recent Evidence Report on Pharmacological and Surgical Treatment of Obesity, the Agency for Health Research and Quality states that the data were considered to be so conclusive regarding the superiority of surgical therapy to existing pharmaceutical and diet therapies in patients with a body mass index (BMI) greater than 40 kg/m^2 that, in the absence of significant advances in medical therapies, comparative studies were not considered to be warranted [15]. Given the limited weight loss associated with even the best studies of non-surgical approaches, it would be difficult to recruit extremely obese subjects willing to be randomized and to have equipoise on the part of clinicians [16].

The use of a non-randomized comparator group including people who did not have bariatric surgery was also considered. However, several limitations of that approach make it difficult to interpret results. These include differences between those who do and who do not go to surgery, including physical and mental health issues, differences in socioeconomic status, and underlying physician or patient motivation all of which may affect results and limit the ability to generalize the findings.

Given these difficulties and finite resources, the LABS consortium determined that high priority scientific questions could be most efficiently addressed by creating an extensive database to test and to explore hypotheses related to bariatric surgical outcomes. The limitations of such an observational approach were also considered. Optimally, data should be collected prospectively and in sufficient detail to measure known and currently unknown factors related to outcomes. LABS investigators attempted to standardize definitions of data items and data collection procedures. Common protocols were designed to include specific data collection time points, data collection instruments, and methods for computerizing data collection, entry, and analysis. Manuals of operations and procedures were created that defined each data element and provided instructions for collection. Data collectors, including study coordinators and surgeons, underwent training and certification with respect to protocols and data collection definitions prior to collecting any data for LABS. Data elements included breaking down each of the surgical procedures into its component parts ("surgical procedural components", e.g. length of alimentary limb, pouch size) and structuring a measuring scheme for each. Extensive quality control procedures were put into place and procedures to identify and correct faulty data implemented. Frequent contact between DCC and Clinical Center staffs, including site visits, help to assure complete and accurate data collection. Operations memos to clarify or modify procedures are distributed to all relevant study personnel to maintain consistency in data collection across sites.

Overview of LABS' Goals

The goals of the LABS study are to assess the risks and health benefits associated with bariatric surgery and to identify aspects of the procedures as well as patient characteristics that are associated with optimal outcomes. To achieve these goals, LABS investigators defined a range of several relevant outcome domains in bariatric surgery. Whenever possible, LABS includes objective measures of patient status and co-morbid disease burden. When objective measures of disease (e.g. – 24 hour pH testing for gastroesophageal reflux) are not feasible, validated and standardized data collection instruments are used, if available. Investigators sought to identify existing data collection instruments which are psychometrically sound. When validated data collection instruments were not available, LABS investigators created new instruments appropriate for patients undergoing bariatric surgery or adapted questionnaires from other clinical studies.

The LABS study is organized into three phases, termed respectively LABS-1, LABS-2, and LABS-3. LABS-1 includes all patients who are at least 18 years of age and who undergo bariatric surgery at participating centers by LABS-certified surgeons. The primary goal of LABS-1 is the evaluation of the short-term **safety** of bariatric surgery. The primary endpoints include important adverse outcomes, such as death and percutaneous or operative re-intervention, that occur within 30 days of operation. A limited dataset of patient and operative characteristics is gathered to describe the frequency of these events in different subgroups and to assess the relationship between adverse outcomes and patient and operative characteristics. The sample size for LABS-1 was selected to be able to obtain precise estimates of safety events (e.g. 30-day mortality), and to have at least 80% power to identify a two-fold (or greater) increase in the risk of 30-day mortality, re-interventions, or

deep vein thrombosis/pulmonary embolism between important subgroups (e.g. men vs. women, BMI under 50 kg/m^2 vs. BMI at least 50 kg/m^2). (LABS-1 forms)

The primary goal of LABS-2 is to evaluate the longer-term safety and **efficacy** of bariatric surgery and to more comprehensively evaluate patient characteristics as they relate to short- and intermediate-term outcomes. The sample size for LABS-2, approximately 2400 patients, was determined to be able to detect "small" effect sizes [17] for continuous outcomes (e.g. change in excess body weight), and at least a two-fold increase or decrease in incidence or prevalence for categorical efficacy outcomes (e.g. resolution of diabetes). In as much as LABS was designed to address multiple hypotheses, many of which are exploratory, adjustments for multiple comparisons did not enter into the sample size calculation. When appropriate for particular analyses, such adjustments will be considered and implemented. The sample size, which provides adequate statistical power to detect differences in occurrence of some uncommon events in relatively small subgroups, will be adequate to allow such adjustment when events are more common or subgroups are larger. To address the aims of LABS-2, the extensive collection of demographic, anthropometric, clinical, behavioral, surgical, and post-surgical care variables will be used to determine their associations with outcomes. Data will be collected prior to surgery, during the surgery, and post-surgery (30 days, 6-month, 1-year, 2-year follow-up visits). LABS-3 will involve further subsets, determined in composition and size by the hypotheses underlying the mechanisms to be studied, of patients from the LABS-2 cohort. One LABS-3 study measures psychosocial and behavioral aspects of obesity, such as quality of life whereas a second LABS-3 study examines the mechanisms underlying diabetes resolution. A proposed third LABS-3 study will assess changes in health economic outcomes and resource utilization. Other aspects of the pathophysiology of obesity and obesity-related diseases will be studied, either through additional sub-studies or by separately funded Ancillary Studies approved by the LABS Ancillary Studies Subcommittee (Funded LABS Ancillaries & ASC guidelines).

Approach to Define the Operative Procedures

While there are several different types of bariatric procedures, the Roux-en-Y gastric bypass (RYGB) is the most commonly performed in the US [18]. The restrictive laparoscopic adjustable gastric band (LAGB) is increasingly used in the US [19]. The biliopancreatic diversion (BPD), with or without the duodenal switch (BPD DS), has also grown in use. Finally, some LABS centers perform a planned two-stage procedure in very high risk, extremely obese patients in which a BPD or BPD DS follows an initial gastric sleeve. There is widespread variability among surgeons in the ways RYGB and BPD are performed. Different approaches to the size of the gastric pouch, length of the alimentary limb, method of anastomotic construction, and extent of nerve interruption of the stomach may or may not have important roles in postoperative outcomes. Thus, any data-gathering project in bariatric surgery that aims to link procedural characteristics with outcomes must acknowledge such variability and either standardize the intervention or measure it with enough detail to assess and analyze the variation. The LABS study elected the latter approach, and will measure each aspect of this variation in detail.

Although the placement of the LAGB is more standardized, the methods and strategies for post-procedural band adjustment also vary considerably between practitioners. This is particularly important for post-procedural interventions in the LAGB where it has been demonstrated that adjustments (rather than the band alone) are the key to effective weight loss [20]. This may also be relevant for RYGB and BPD, where behavioral and dietary interventions before and after the procedure may have important effects on the outcome. If unmeasured, the impact of these pre-, peri-, and post-procedural components of bariatric

surgery might inappropriately be ascribed to the procedure itself. LABS will not standardize surgical procedures or pre- or post operative care, per se, but rather will attempt to measure and then describe this variability through strictly defined and enforced/audited data collection and analysis.

Approach to Assessing Outcome Domains in Bariatric Surgery

The short- and longer-term risks of bariatric surgery differ with aspects of the procedure [21] and in relation to patient characteristics, such as age, sex, and co-morbidities [9,22,23]. A complete assessment of bariatric surgery involves ascertaining its impact on patient health, well-being, quality of life, and health care utilization. For descriptive purposes, LABS investigators have clustered outcomes into "safety" and "non-safety" domains, The terminology involved in describing untoward events has been problematic within the field of bariatric surgery. Anastomotic complications are of primary interest in the RYGB and BPD procedures. However, there are no universally agreed-upon definitions [24]. To assess which anastomotic complications clinicians consider to be clinically significant, LABS investigators developed a measurement scheme to record all POR and details of the presumed and confirmed reasons. For standardization, LABS has an Adjudication Committee that will review and classify all deaths and those surgical re-operations and unplanned post-discharge anticoagulation therapies for which the reason could not be confirmed.

The limited dataset of LABS-1 was designed to describe the frequency of interventions or hospitalizations occurring within 30 days after bariatric surgery and factors associated with those events and with death. The duration of post-procedure surveillance for important adverse outcomes determines the number and types of events identified. Administrative claims demonstrate that data analyses looking only at in-hospital mortality miss approximately half of the deaths within 30-days of gastric bypass [22]. The appropriate time window to describe a post-surgical event remains unclear. By convention, events occurring within 30-days after operation are considered surgically related.

The LABS-2 dataset was designed to measure and evaluate longer-term outcomes and to evaluate the efficacy of bariatric surgery. Key groups of "non-safety" outcomes for LABS-2 include (but are not limited to) weight loss, changes in body composition, functional impairment, psychosocial function (including quality of life), cardiovascular, metabolic, pulmonary, renal, musculoskeletal, urogynecologic, reproductive, and gastrointestinal outcomes.

Risk stratification

Risk stratification is a useful tool to put safety measures into context. Currently, there is no evidence-based scheme for risk stratification in bariatric surgery. Acquiring the broad evidence base to support the development of such a risk-stratification tool is one of the goals of LABS. Administrative claims and case series data suggest that older patients and males have higher risk of perioperative death than younger patients and females, respectively [23,25]. However, little is known about other patient or procedural factors that relate to outcomes. LABS-1 and LABS-2 will study the extent to which patient demographic characteristics, BMI, co-morbid conditions, medication use and physiologic status relate to these outcomes. From this evidence-base of associated factors, LABS investigators plan to provide the evidence and elements for a meaningful risk stratification/adjustment strategy. Since many poor surgical outcomes are relatively infrequent events, a large study cohort is necessary to define a risk stratification scheme.

LABS-1 is testing the following risk assessment hypotheses: that men have higher rates of POR and 30-day mortality rate than women, that greater BMI is associated with higher rates of VTE, POR and 30-day death, and that wound infection is more common among open than laparoscopic procedures. Furthermore, the severity of various co-morbidities, collected on all participants in LABS-1, will be examined for association with poor outcomes (LABS-1 Pre-Operative form). LABS-2 includes more detailed measures of severity than LABS-1 and analyses will help determine if they are more predictive of events than the less detailed measures used in LABS-1. Other hypotheses to be tested in LABS-2 include whether other, more detailed, patient factors and characteristics of the surgical procedure ("surgical procedural components") are related to outcome.

Outcome Domains in Bariatric Surgery

The outcome domains studied in LABS-2 and described below are listed in Table 1. This comprehensive evaluation of outcomes resulted from the consortium's collaborative efforts in structuring a thorough, yet feasible and standardized, database. Table 2 outlines the standard forms and measures used in LABS-2 to assess each of these domains as well as the contact time points at which they will be administered. Even more detailed information on each of these outcome domains along with the definitions and specific measures used can be found on the links within Table 2 or, if applicable, the text of this manuscript.

Weight Loss and Body Composition

The primary intent of bariatric procedures is to induce weight loss by limiting intake and to promote behavioral changes in overall energy balance that result in significant and sustained decreases in weight. LABS-2 will measure weight at each of the annual follow-up visits using a standard scale (Tanita model #TBF-310H01A). The LABS investigators hypothesize that men will experience greater weight loss than women and that there is a direct relationship between physical activity and weight loss at follow-up intervals. We also hypothesize that diabetic patients will lose less weight and that a longer length of bypassed limb in gastric bypass surgery is associated with greater weight loss maintenance [26,27]. (LABS Physical Measurements Protocol)

Diabetes Mellitus and Insulin Resistance

Type 2 diabetes mellitus (T2DM), the metabolic syndrome, and insulin resistance syndrome (IRS) are common metabolic co-morbidities of obesity. Many case series have demonstrated significant and sustained improvements in these parameters after weight loss procedures [6] but measures of these parameters in large cohorts have been limited. LABS-2 will evaluate the longer-term efficacy of bariatric surgery with respect to T2DM based on a clinical history of medication use and on serial measurements of fasting blood glucose, and HbA1c. Assessing efficacy for preventing or resolving the metabolic syndrome and IRS will be based on fasting glucose, insulin, lipoprotein profiles, resting blood pressure, and waist circumference. It is hypothesized that improvement in T2DM, metabolic syndrome, and IRS will be related to degree of weight loss, degree of loss of fat mass, and level of physical activity at follow up [28,29].

Cardiovascular and Pulmonary Disease

Obesity is a major risk factor for cardiovascular diseases (CVD) and obstructive sleep apnea and has been increasingly recognized in patients with extreme obesity [6,30-35] The prevalence of sleep apnea and changes from baseline status will be assessed by self-report through the use of the Berlin Sleep Questionnaire [36] and by the reported use of positive airway pressure devices. It is hypothesized that weight loss and reductions in neck circumference will be associated with improvements in sleep apnea. To assess the efficacy of bariatric surgery to

reduce risk for CVD, LABS-2 will measure C-reactive protein, lipoprotein profiles, resting blood pressure, waist circumference, and clinical history of medication use. It is hypothesized that improvement in CVD risk factors will be related to the magnitude of weight loss, loss of fat mass, and lower BMI post-surgery [37]. Furthermore, change in cardiac function will be measured by the time to complete a 400-meter corridor walk. It is hypothesized that this will be related to age, BMI, sex, and other factors.

Renal Disease

Obesity causes and complicates diabetes and hypertension, the two most common causes of kidney failure[38]. In addition, there are several mechanisms by which obesity may independently and negatively impact renal function such as by adipogenic hormones that may have direct injurious actions on the kidney [39]. However, bariatric surgery itself has been associated with progressive renal disease through a variety of mechanisms [40], and may also contribute to the development of renal calculi. For these reasons LABS-2 will measure renal function by serum creatinine and cystatin and urinary albumin and creatinine, and will assess the prevalence of diagnosed nephrolithiasis at baseline and follow-up. It is hypothesized that albuminuria will diminish after successful bariatric surgery and that renal function as measured by serum creatinine will remain stable after successful surgery.

Liver Function

Another problem of growing public health concern is the increased prevalence of non-alcoholic fatty liver disease (NAFLD) in obese populations [41] and the growing identification of NAFLD when evaluated by liver biopsy in patients undergoing a bariatric surgical procedure [42]. There are limited data available defining the prevalence and severity of steatohepatitis (NASH), as assessed by intra-operative liver biopsy, in extremely obese persons undergoing bariatric surgery, although NASH is an increasingly recognized cause of “cryptogenic” cirrhosis [43]. It is hypothesized that the prevalence and severity of NASH is underestimated by traditional clinical measures and that liver disease severity will be correlated with short-term post-surgical morbidity. We also hypothesize that increased liver size at the time of operation is associated with a higher rate of failed laparoscopic approaches to bariatric procedures.

Behavioral/Psychosocial Factors

Evidence suggests that pre-existing psychological and behavioral factors may influence outcomes following bariatric surgery [44]. It is hypothesized that patients who have active, untreated substance abuse, binge eating, or depression at baseline will experience higher rates of post-surgical medical complications and less weight loss [45,46]. Conversely, those subjects who intentionally lose weight prior to operation will achieve greater weight loss in the short and longer term [47]. Behavioral measures will be assessed at both baseline and follow-up, and will include questions on pre-surgery weight loss practices and eating patterns (including binge eating and eating beyond satiation), tobacco and alcohol use, history of psychiatric disorders, and counselor/therapist contact. Depressive symptoms will be assessed by the Beck Depression Inventory, Version 1 [48]. Objective measures of physical activity will be assessed by the STEPWATCH 3 Step Activity Monitor (www.cymatech.com) at baseline and follow-up visits.

Musculoskeletal and Functional Status

Osteoarthritis, either caused or aggravated by obesity, is a major limiting comorbid condition among the population of patients undergoing bariatric surgery. Functional limitations due to back, hip, and knee joint degeneration is a leading cause of functional decline, use of durable medical goods (wheel chairs, walkers, electric scooters) and impaired

quality of life. LABS investigators will test the hypothesis that functional status will improve with surgery and the extent of improvement will be associated with the degree of weight loss. In addition, we will investigate whether functional limitations prior to surgery are linked to poor outcomes following the bariatric procedure. Functional status will be assessed in LABS through a combination of self-reports (walking ability, use of assistance devices) as well as a timed corridor walk.

Gender Issues

Obesity affects all aspects of well-being including those that are gender specific. There are also potential gender differences in the longer-term efficacy of bariatric surgery. For example, obesity is a known risk factor for several health conditions specific to and prevalent among women such as menstrual abnormalities, infertility [49], and urinary incontinence [50]. It is hypothesized that menstrual abnormalities, fertility, urinary incontinence, and symptoms of polycystic ovarian diseases will improve following bariatric surgery. These will be assessed by several questionnaires.

Nutrient Deficiencies

Another potential long-term risk of bariatric surgery is nutrient deficiency [51]. LABS-2 will be able to investigate micro- and macro-nutrient deficiencies by surgical procedure by hypothesizing more frequent occurrences with malabsorptive procedures [26,52] and by various components of surgery such as roux limb length and pouch size. Plasma and serum samples will be stored in a specimen repository for future analysis of macro and micronutrients.

Economic Impact

Workers who are obese have a high prevalence of work limitations [53] and severe obesity increases the number of work loss days and is an important factor in the workplace [54,55]. The effects of weight loss surgery on productivity at work, absenteeism and presenteeism are not well studied. LABS will administer several validated questionnaires to assess this impact including the Work Productivity and Activity Impairment (WPAI) form V2.0 [56]. It is hypothesized that patients undergoing surgery will lose fewer days of work and that productivity at work will improve after surgery.

Biospecimens

Blood and urine specimens will be obtained from LABS-2 participants at baseline, and post-operatively at 6 months, 12 months and annually thereafter. Aliquots of whole blood, plasma, and serum will be banked in the NIDDK Biospecimens Repository for future investigations into factors such as changes in metabolic parameters and markers of risk. An additional quantity of whole blood will be drawn to be used for future DNA analysis, with appropriate consents. These specimens will be a major resource for funded, LABS-associated Ancillary Studies. Non-LABS investigators may also request access to these biospecimens through application via the LABS ancillary studies process.

Conclusion

The goal of the LABS consortium is to accelerate clinical research and progress in understanding the pathogenesis of extreme obesity and its complications, as well as in understanding the risks and benefits of bariatric surgery as a treatment modality. Through the use of standardized definitions, high fidelity data collection, and the use of validated measurement instruments, LABS investigators aim to enhance the ability of clinicians to

provide meaningful evidence-based recommendations for patient evaluation, selection for surgery, and follow-up care.

Extreme obesity affects nearly every organ system and many aspects of the human experience. A comprehensive assessment of surgical treatments for obesity must assess multiple facets in as objective a manner as is possible. At present there are no multi-site datasets that capture comprehensive predictors and outcomes of bariatric surgery with fidelity. The data being collected by LABS, and described herein and on the LABS website, should help to provide researchers with standardized measurement instruments that can be used across centers. LABS investigators hope to provide evidence to assess the broad impact of these operations on patients and the healthcare system. Future reports will detail results and progress in these areas.

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Standard Abbreviations

NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
DCC	Data Coordinating Center
LABS	Longitudinal Assessment of Bariatric Surgery
RCTs	Randomized Controlled Trials
RYGB	Roux-en-Y gastric bypass
LAGB	Laparoscopic Adjustable Gastric Band
BPD	Biliopancreatic diversion
BPD DS	Biliopancreatic diversion with duodenal switch
VTE	Venous thromboembolism
POR	Percutaneous / operative reintervention
T2DM	Type 2 diabetes mellitus
IRS	Insulin resistance syndrome
CVD	Cardiovascular disease
NAFLD	Nonalcoholic fatty liver disease
NASH	Nonalcoholic steatohepatitis

References

1. Wadden TA, Sternberg JA, Letizia KA, et al. Treatment of obesity by very low calorie diet, behavior therapy, and their combination: a five-year perspective. Int J Obes. 1989; 13:39–46. [PubMed: 2613427]
2. Dansinger ML, Gleason J, Griffith J, et al. Comparison of the Atkins, Ornish, Weight Watchers, and Zone Diets for Weight Loss and Heart Disease Risk Reduction. JAMA. 2005; 293:43–53. [PubMed: 15632335]
3. Yanovski SZ, Yanovski JA. Obesity. N Engl J Med. 2002; 346:591–602. [PubMed: 11856799]

4. Safer DJ. Diet, behavior modification, and exercise: a review of obesity treatments from a long-term perspective. South Med J. 1991; 84:1470–74. [PubMed: 1749981]
5. Pories WJ, Flickinger E, Meelheim D, et al. The effectiveness of gastric bypass over gastric partition in morbid obesity: consequence of distal gastric and duodenal exclusion. Annals of Surgery. 1982; 196:389–99. [PubMed: 7125726]
6. Buchwald H, Avidor Y, Braunwald E, et al. Bariatric surgery: a systematic review and meta-analysis. JAMA. 2004; 292:1724–37. [PubMed: 15479938]
7. Torgerson J, Sjostrom L. The Swedish Obese Subjects (SOS) study - rationale and results. International Journal of Obesity. 2001; 25:S2–S4. [PubMed: 11466577]
8. Pories, W. Estimate by the American Society for Bariatric Surgery. 2006. Ref Type: Personal Communication
9. Encinosa WE, Bernard DM, Steinger CA, et al. Use and costs of bariatric surgery and prescription weight-loss medications. Health Affairs. 2005; 24:1039–47. [PubMed: 16012144]
10. Gastrointestinal surgery for severe obesity: National Institutes of Health Consensus Development Conference Statement. Am J Clin Nutr. 1992; 55:615S–19S. [PubMed: 1733140]
11. NIDDK Working Group on Bariatric Surgery: Executive Summary. NIDDK; 2002. Ref Type: Electronic Citation
12. Sugerman HJ, Starkey JV, Birkenhauer R. A randomized prospective trial of gastric bypass versus vertical banded gastroplasty for morbid obesity and their effects on sweets versus non-sweets eaters. Annals of Surgery. 1987; 205:613–24. [PubMed: 3296971]
13. Nguyen NT, Goldman C, Rosenquist CJ, et al. Laparoscopic versus open gastric bypass: a randomized study of outcomes, quality of life, and costs. Annals of Surgery. 2001; 234:279–91. [PubMed: 11524581]
14. Kral JG. Swedish obese subjects study - best available data to support antiobesity surgery? Surg Obes Relat Dis. 2006; 2:561–64. [PubMed: 17015212]
15. Maggard MA, Shugarman LR, Suttorp M, et al. Meta-analysis: surgical treatment of obesity. Annals of Internal Medicine. 2005; 142:547–59. [PubMed: 15809466]
16. Courcoulas A, Flum D. Filling in the gaps in bariatric surgical research. JAMA. 2005; 294:1957–60. [PubMed: 16234502]
17. Cohen, J. Statistical power analysis for the behavioral sciences. Lawrence Earlbaum Associates; Hillsdale, NJ: 1988.
18. Nguyen NT, Root J, Zainabadi K. Accelerated growth of bariatric surgery with the introduction of minimally invasive surgery. Arch Surg. 2005; 140:1198–1202. [PubMed: 16365242]
19. O'Brien PE, Dixon JB. Weight loss and early and late complications - the international experience. American Journal of Surgery. 2002; 184:42S–5S. [PubMed: 12527350]
20. Shen R, Dugay G, Rajaram K, et al. Impact of patient follow-up on weight loss after bariatric surgery. Obesity Surgery. 2004; 14:514–19. [PubMed: 15130229]
21. Deveney CW, MacCabee D, Marlink K, et al. Roux-en-Y divided gastric bypass results in the same weight loss as duodenal switch for morbid obesity. American Journal of Surgery. 2004; 187:655–59. [PubMed: 15135686]
22. Flum DR, Salem L, Elrod JA, et al. Early mortality among medicare beneficiaries undergoing bariatric surgical procedures. JAMA. 2005; 294:1903–08. [PubMed: 16234496]
23. Raftopoulos I, Schuchert M, Luketich J, et al. Advanced age and sex as predictors of adverse outcome following gastric bypass surgery. Journal of the Society of Laparoscopic Surgeons. 2005; 9:272–76.
24. Schauer PR, Ikramuddin S, Gourash W, et al. Outcomes for laparoscopic Roux-en-y gastric bypass for morbid obesity. Ann Surgery. 2000; 232:515–29.
25. Flum D, Dellinger EP. Impact of gastric bypass operation on survival: a population-based analysis. J American Coll of Surgeons. 2004; 199:543–551.
26. Brolin RE, LaMarca LB, Kenler HA, et al. Malabsorptive Gastric Bypass in Patients with Superobesity. Journal of Gastrointestinal Surgery. 2002; 6:195–205. [PubMed: 11992805]

27. Choban PS, Flancbaum L. The Effect of Roux Limb Lengths on Outcome after Roux-en-Y Gastric Bypass: A Prospective, Randomized Clinical Trial. Obesity Surgery. 2002; 12:540–45. [PubMed: 12194548]
28. Orchard TJ, Temprosa M, Goldberg R, et al. The Effect of Metformin and Intensive Lifestyle Intervention on the Metabolic Syndrome: The Diabetes Prevention Program Randomized Trial. Annals of Internal Medicine. 2005; 142:611–19. [PubMed: 15838067]
29. Sjostrom CD, Lissner L, Wedel H, et al. Reduction in incidence of diabetes, hypertension and lipid disturbances after intentional weight loss induced by bariatric surgery: the SOS intervention study. Obes Res. 1999; 7:477–84. [PubMed: 10509605]
30. de Leiva A. What are the benefits of moderate weight loss? Exp Clin Endocrinol Diabetes. 1998; 106:10–13. [PubMed: 9792475]
31. Giusti V, De Lucia A, Di Vetta V, et al. Impact of Preoperative Teaching on Surgical Option of Patients Qualifying for Bariatric Surgery. Obesity Surgery. 2004; 14:1241–46. [PubMed: 15527642]
32. Infanger D, Baldinger R, Branson R, et al. Effect of Significant Intermediate-term Weight Loss on Serum Leptin Levels and Body Composition in Severely Obese Subjects. Obesity Surgery. 2003; 13:879–88. [PubMed: 14738675]
33. Koch M, Rett EM, Volk A, et al. The PPAR2 amino acid polymorphism Pro 12 Ala is prevalent in offspring of Type II diabetic patients and is associated to increased insulin sensitivity in a subgroup of obese subjects. Diabetologia. 1999; 42:758–62. [PubMed: 10382597]
34. Valencia-Flores M, Orea A, Herrera M, et al. Effect of Bariatric Surgery on Obstructive Sleep Apnea and Hypopnea Syndrome, Electrocardiogram, and Pulmonary Arterial Pressure. Obesity Surgery. 2004; 14:755–62. [PubMed: 15318977]
35. Vendrell J, Broch M, Vilarrasa N, et al. Resistin, Adiponectin, Ghrelin, Leptin, and Proinflammatory Cytokines: Relationships in Obesity. Obes Res. 2004; 12:962–71. [PubMed: 15229336]
36. Netzer NC, Stoohs RA, Netzer CM, et al. Using the Berlin Questionnaire to identify patients at risk for the sleep apnea syndrome. Annals of Internal Medicine. 1999; 131:485–91. [PubMed: 10507956]
37. Blumenthal JA, Sherwood A, Gullette EC. Exercise and weight loss reduce blood pressure in men and women with mild hypertension: effects on cardiovascular, metabolic, and hemodynamic functioning. Arch Intern Med. 2000; 160:1947–58. [PubMed: 10888969]
38. Wiggins KJ, Johnson DW. The influence of obesity on the development and survival outcomes of chronic kidney disease. Adv Chronic Kidney Dis. 2005; 12:49–55. [PubMed: 15719333]
39. Coresh J, Astor B, Sarnak MJ. Evidence for increased cardiovascular disease risk in patients with chronic kidney disease. Curr Opin Nephrol Hypertens. 2004; 13:73–81. [PubMed: 15090863]
40. Khurana RN, Baudendistel TE, Morgan EF, et al. Postoperative rhabdomyolysis following laparoscopic gastric bypass in the morbidly obese. Arch Surg. 2004; 139:73–76. [PubMed: 14718280]
41. Haynes P, Liangpunsakul S, Chalasani N. Nonalcoholic fatty liver disease in individuals with severe obesity. Clin Liver Dis. 2004; 8:535–47. [PubMed: 15331062]
42. Abrams GA, Kunde SS, Lazenby AJ, et al. Portal fibrosis and hepatic steatosis in morbidly obese subjects: a spectrum of nonalcoholic fatty liver disease. Hepatology. 2004; 40:475–83. [PubMed: 15368453]
43. Burke A, Lucey MR. Non-alcoholic fatty liver disease, non-alcoholic steatohepatis and orthotopic liver transplantation. Am J Transplant. 2004; 4:686–693. [PubMed: 15084161]
44. Herpetz S, Kielmann R, Wolf AM, et al. Do psychosocial variables predict weight loss or mental health after obesity surgery? A systematic review. Obes Res. 2004; 12:1554–69. [PubMed: 15536219]
45. Hsu LK, Betancourt S, Sullivan SP. Eating disturbances before and after vertical banded gastroplasty: a pilot study. Int J Eat Disord. 1996; 19:23–34. [PubMed: 8640199]
46. Hsu LK, Benotti PN, Dwyer J, et al. Nonsurgical factors that influence the outcome of bariatric surgery: a review. Psychosom Med. 1998; 60:338–46. [PubMed: 9625222]

47. Alvarado R, Alami RS, Hsu G, et al. The impact of preoperative weight loss in patients undergoing laparoscopic Rouex-en-Y gastric bypass. Obesity Surgery. 2005; 15:1282–89. [PubMed: 16259888]

48. Beck AT, Ward CH, Mendelson M, et al. An inventory for measuring depression. Archives of General Psychiatry. 4:561–71. 21961. [PubMed: 13688369]

49. Norman RJ, Noakes M, Wu R, et al. Improving reproductive performance in overweight/obese women with effective weight management. Hum Reprod Update. 2004; 10:267–80. [PubMed: 15140873]

50. Kapoor DS, Davila GW, Rosenthal RJ, et al. Pelvic floor dysfunction in morbidly obese women: pilot study. Obes Res. 2004; 12:1104–07. [PubMed: 15292474]

51. Alvarez-Leite JI. Nutrient deficiencies secondary to bariatric surgery. Curr Opin Clin Nutr Metab Care. 2004; 7:569–575. [PubMed: 15295278]

52. Faintuch J, Matsuda M, Cruz ME, et al. Severe protein-calorie malnutrition after bariatric surgery. Obesity Surgery. 2004; 14:175–81. [PubMed: 15018745]

53. Hertz RP, Unger AN, McDonald M, et al. The impact of obesity of work limitations and cardiovascular risk factors in the U.S. workforce. J Occup Environ Med. 2004; 46:1196–1203. [PubMed: 15591970]

54. Bungum T, Satterwhite M, Jackson AW, et al. The relationship of body mass index, medical costs, and job absenteeism. Am J Health Behav. 2003; 27:456–62. [PubMed: 12882439]

55. Pronk NP, Martinson B, Kessler RC, et al. The association between work performance and physical activity, cardiorespiratory fitness, and obesity. J Occup Environ Med. 2004; 46:19–25. [PubMed: 14724474]

56. Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. PharmacoEconomics. 1993; 4:353–65. [PubMed: 10146874]

Table 1

Outcome Domains in Bariatric Surgery

- Weight Loss and Body Composition
- Diabetes Mellitus and Insulin Resistance
- Cardiovascular and Pulmonary Disease
- Renal Disease
- Liver Function
- Behavioral/Psychosocial Factors
- Musculoskeletal and Functional Status
- Gender Issues
- Nutrient Deficiencies
- Economic Impact

LABS-2 Form Name / Details*	Baseline	Baseline Update	Time of Annually	30-days	6-mo. Followup	12-mo / Discharge
Central (includes urine) , Local, Repository, Pathology Forms	X				X	X
400-Meter Eligibility Form	X					X
400-Meter corridor walk form	X					X
Medication form	X	X			X	X
Stepwatch Activity Diary	X					X
Surgeons Medical Assessment	X					X
Post-surgical Hospital Discharge Questions			X			
Post-Operative Evaluation Form				X		
Health Care Utilization Form					X	X
6-month Follow-up Form					X	
Research Coordinator Assessment	X	X				X
Demographic Information Questions	X					X
Pre-Bariatric Weight Loss Questions	X	X				
Questions from Goals and Relative Weights Questionnaire (GRWQ)	X	X				
Weight Control Practices	X					X
Questionnaire on Eating/Weight Patterns (QEWP-R)	X					X
Weight Loss Practices & Eating Habits (L, AHEAD)	X					X
Eating Beyond Satiation	X					X
Tobacco use	X					X
Alcohol use (AUDIT)	X					X
Substance Abuse	X					X
Beck Depression Inventory (BDI) **	X				X	X
Interpersonal Support Evaluation List (ISEL-12)	X					X
Short Form Health Survey (SF-36)	X				X	X
Work Productivity and Activity Impairment (WPAI:GH)	X					X
Psychiatric & Emotional Test Survey	X					X
Impact on Weight Questionnaire (IWQOL – Lite)	X					X
Gastrointestinal Symptoms Response Scale (GSRS)	X					X
Urinary Incontinence Questionnaire	X					X
Berlin Sleep Questionnaire	X					X
Sexual Function Questionnaire	X					X
Reproductive Health Questionnaire	X					X
Self-assessment Medical Assessment	X					X
Western Ontario and McMaster's University (WOMAC) Osteoarthritis Index	X					X
Michigan Neuropathy Screening Instrument	X					X

* Since the LABS data collection system is a dynamic system, some definitions/details may be missing due to form modifications which are currently in process.

** Links to standardized forms which LABS uses in full and provides references for in the main article, are not provided. Standardized forms not mentioned in the text are linked from this table. These include ISEL-12, SF-36, IWQOL-Lite, and the GSRS. Prospective users should contact the appropriate personnel to obtain permission to use these forms.