Filling the Gaps in Bariatric Surgical Research

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DESPITE PHENOMENAL GROWTH IN THE USE OF BARiatric surgical procedures, research on these interventions continues to be reported primarily through the case series of experienced practitioners[1] and has focused only on selected outcomes. As a result, there is a gap between the proliferation of these procedures and the evidence base needed to understand key components of their use. This gap includes an assessment of the effectiveness of bariatric surgery in the population at-large, the total impact of bariatric surgery on patients and the health care system, identification of which patients are best suited for which procedures, and the physiological mechanisms that promote weight loss after surgery. Understanding the circumstances that have limited research in bariatric surgery should help direct future investigators to the challenges that need to be addressed when studying this important and increasingly performed group of procedures.

Randomized Trials in Bariatric Surgery

Perhaps the most important barrier to effective bariatric surgical research has been the absence of an adequate control group. Because much of obesity appears to be mediated by individual factors (ie, genetic profile, resting energy expenditure, motivation, activity level, and ingested calories), failure to control for these and other features when comparing cohorts makes it difficult to determine the effect of the intervention. The best way to control for differences between patients is to randomize obese patients to an operative or nonoperative intervention. While randomized trials of procedural modifications have been performed,[2] the broader question of the utility of bariatric surgery compared with nonoperative treatment has been more difficult to assess in this way. For example, a randomized trial[3] of a weight-loss procedure compared with usual therapy was performed in the 1970s, but it had significant ethical problems (ie, lack of informed consent, deception of patients). A more recent randomized trial[4] compared adjustable gastric banding with a low-calorie diet and included patients who were below the standard weight criteria for bariatric surgery because the ethics committee determined that the trial would have been unethical in more obese patients.

There are significant barriers to conducting randomized trials of bariatric surgery. Many surgeons believe that genuine clinical equipoise does not exist between operative and nonoperative options and therefore consider randomization to be unethical.[5] Payers may be reluctant to fund expensive interventions in the context of research trials when there is a potential for lifelong complications that could require further financial resources. Patients who are considering bariatric surgery may not agree to randomization because they have spent a lifetime in the "nonintervention arm" especially if they have other means to access a surgical option. Patients who are willing to participate in bariatric surgery trials may not have any other means to finance the procedure; for these patients, a randomized trial is their only opportunity for the procedure, which may be considered coercive. For example, Louisiana offered bariatric surgery to 40 randomly selected state employees drawn from a larger pool of interested surgical candidates who were participating in nonoperative weight-loss strategies.[6] Both groups are being followed up over time to assess the costs associated with these 2 approaches.

Moreover, randomization to interventions with significant differences in the nature and timing of risk raises ethical problems involving informed and voluntary consent. It is unclear whether a decision to participate in a randomized trial can be made in a truly informed manner because of the differences between the anticipated long-term risks of nonoperative interventions (progressive weight gain and its effect on organ systems) and the short-term and potentially life-threatening operative risks. Although this level of informed decision making is assumed in clinical care, a higher standard may be required for this type of randomized intervention.

Generalizability of Bariatric Surgical Interventions

Other aspects of bariatric surgical care make clinical research in this area problematic. The use of administrative data is limited because coding has not kept pace with advances in surgery. Imprecise coding schemes often are used

See also pp 1909, 1918, and 1960.

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to describe more than 1 type of procedure. For example, the use of "unlisted laparoscopy" codes to identify laparoscopic cases may capture only 20% to 40% of the procedures[7] and only this year has a *Current Procedural Terminology* code for laparoscopic gastric bypass been developed.

Case series of the competing surgical interventions suggest that almost all interventions are reportedly safe and effective in the hands of the surgeon. However, generalizability of these results is limited due to the lack of standardization in the technical components that define different types of bariatric procedures and the way that these procedures are described. For example, in stomach-restricting procedures, variation in gastric pouch size is often not reported, and technical variations in intestinal limb length, vagus nerve preservation, and other procedure-specific differences may contribute to the outcomes observed but are variably performed and commonly not reported. The issue of procedural standardization might be better addressed by using an animal model to determine the critical components of the various bariatric surgical procedures, but such a model has been only occasionally used.[8] Animal models might help to identify the specific components of the procedures that should be reproduced and also would facilitate an exploration of the neurohormonal components of bariatric surgery that 1 day may be imitated by a nonsurgical, pharmacological approach.

Another important limit to generalizability is that bariatric procedures often achieve weight loss through perioperative behavioral interventions, including presurgical education, active support groups, other multidisciplinary activities, and close follow-up. These additional interventions are inconsistently reported and only occasionally critically evaluated. As a result, it is unclear how these interventions contribute to weight-loss success, and the relative contribution of each of these to certain patient groups remains undefined. Standardizing presurgical education, patient selection, and postsurgical support is essential to avoid important confounding in studies of surgical effectiveness.

Longitudinal Outcome Evaluations

Longitudinal follow-up in bariatric surgical research is essential but in most studies is short-term and incomplete.[1] There are many ways in which this issue undermines the evidence for these procedures. Patients who do not participate in ongoing care (follow-up) may be different from those who do participate and this may limit conclusions about efficacy and safety. Comparative groups of obese patients who did not receive surgery will develop adverse effects of obesity over time and only a longitudinal approach will capture these nonsurgical events.

Additionally, bariatric interventions are often associated with different slopes of weight loss over time and each of the commonly performed procedures has different weight-loss slopes than other procedures (ie, weight loss with adjustable gastric banding may take more time than weight loss with the Roux-en-Y gastric bypass[9]). Both weight regain and long-term operative complications also may occur differentially over time. Furthermore, when patients undergo profound weight loss they enter a state of negative nitrogen balance that affects many other physiological parameters. Studies evaluating the effect of these procedures on physiological parameters need to include data gathered after this period of negative nitrogen balance has ended (this may be 12-18 months for gastric bypass, but this period has not been established for adjustable banding).

In longitudinal analyses, the issue of an adequate control group becomes even more essential because differentiating the effects of obesity from the effects of aging is problematic. In perhaps the best example, the Swedish Obesity Subjects study is a matched cohort of 2000 operative and nonoperative patients who were followed up for more than 10 years.[10] Unfortunately, studies like the Swedish Obesity Subjects study that evaluate surgical fields in evolution may be "outdated" by the time the end point has been achieved. For example, in the Swedish Obesity Subjects study, the procedure primarily being studied was vertical banded gastroplasty (approximately 85% of procedures) but vertical banded gastroplasty is no longer being performed with any frequency because of the relatively inferior weight loss compared with gastric bypass[2] and this may limit generalizability of the study's findings on perioperative risk and survival. Moreover, accomplishing comprehensive and complete follow-up over time as in the Swedish Obesity Subjects study is a burdensome process for patients, is costly for funding agencies, and requires significant research infrastructural support.

Evaluation of Safety

With the growth in the use of bariatric surgery has come increasing scrutiny of its safety. For most individuals, obesity poses a long-term rather than a short-term health risk and therefore many physicians do not consider bariatric surgery to be the standard of care for the morbidly obese patient in the same way colon resection is considered the standard of care for the patient with colon cancer. Although this attitude may change with a greater appreciation of the long-term risks of obesity, the "elective" nature of the bariatric procedure demands a low risk so that it is acceptable when balanced against the immediate alternative. Another reason for increased scrutiny regarding safety is that while laparoscopic approaches have made these procedures attractive to patients, laparoscopic gastric bypass is challenging to perform and has a considerable "learning curve."[11] Media exposure of adverse outcomes at leading medical centers, the closing of bariatric surgery programs because of perceived safety problems, and the sense that inexperienced surgeons and surgical centers are involved in this procedure have made evaluations of bariatric surgical safety paramount.[12]

One problem in the assessment of surgical safety is that outcomes such as death, deep vein thrombosis, and pulmonary embolism occur rarely; therefore, thousands of patients are required to evaluate the patient, surgeon, and pro-

cess components of care that relate to these outcomes. In part because adequate studies are difficult to perform without access to large numbers of treated patients and adequate funding, little is known about the critical components that make up risk stratification in the bariatric surgery population. Most of the relevant studies are challenged by type II errors. Administrative data sets lack clinically relevant variables such as body mass index, comorbid illness severity, and smoking status. Furthermore, the risk-adjustment strategies used with administrative data are limited to those based on *International Classification of Diseases, Ninth Revision, Clinical Modification* codes and the number of codes included as well as the timing and inclusion of these conditions or events before or after operation may be problematic. The lack of in-depth and clinically based risk-adjustment information and the rarity of the adverse outcomes have made it virtually impossible to compare procedures, institutions, and surgeons for safety outcomes in bariatric surgery.

The incompletely understood relationship between surgeon/medical center experience and outcome is a particularly important example of how difficult it is to compare safety outcomes across surgeons and medical centers. Because of inadequate risk stratification schemes, it is unclear if higher volume surgeons/medical centers appear to have better outcomes because of improved patient selection or referral (excluding the most ill or extremely obese) or because of specific processes of care or personnel training associated with higher volume medical centers. Moreover, because surgical health services researchers have only recently used population-level data to evaluate the risks of bariatric surgery in the "real world," the differences between case series and community-at-large outcomes that have been identified for virtually every area of operative intervention are just now being appreciated for bariatric surgery. These issues require exploration to better understand the differences between "study site" practice and surgical care in the community, and are central to making policy recommendations aimed at improving quality.

Domains of Bariatric Surgical Research

Another challenge in evaluating bariatric surgery is that unlike many other conditions treated by surgeons, obesity affects every organ system and component of well-being. Factors that contribute to obesity and those that are involved in successful weight-loss interventions are mulitfactorial, and can act as confounding features of the intervention as well as potential effect modifiers. Addressing each of these domains and the organ systems affected by obesity requires a more comprehensive approach to prospective research than is typical for clinical research. The organ systems that need to be assessed include those directly involved in obesity and weight loss (ie, cardiovascular, pulmonary, gastrointestinal tract, hepatic, and those related to diabetes) as well as those less commonly linked to obesity such as neurological (ie, pseudotumor cerebri), urological (ie, stress incontinence), musculoskeletal (ie, osteoarthritis and bone demineralization), and others. Beyond the physical domains, other areas affected by bariatric surgical procedures may also be components of the effect of these procedures. These include psychosocial domains (including abnormal eating behaviors, mental illness, interpersonal/sexual relationships, and employment and work-related issues) along with health economic factors (ie, availability of resources, accessibility and use of health care services for follow-up care, home care, multidisciplinary support, special diets, and access and participation in exercise programs).

Comprehensive approaches to research on the impact of bariatric surgery must encompass these varied domains. Unfortunately, such a comprehensive approach is problematic because it requires multiple disciplines to work together, significant resources, and a burden for patients due to time required for follow-up. There is also debate about the best way to "score" many of these domains, including baseline status and changes in status with treatment over time. Objective, reliable, and scaled measures allowing for additional data collection of these domains over time should be used. One challenge to clinical researchers is to develop more objective metrics for many of the domains listed above and then to identify the resources needed to apply these comprehensive assessments to a sufficient number of patients undergoing these procedures to make valid inferences.

Funding and the Future of Bariatric Surgical Research

Research of obesity surgical treatments did not become a priority until the 1990s, and since then has been sponsored mainly by the National Institutes of Health. In both 1991 and 2002, the National Institutes of Health[13,14] helped advance bariatric surgical research by gathering experts to define important unexamined topic areas. In 2003, the National Institute of Diabetes and Digestive and Kidney Diseases initiated its Longitudinal Assessment of Bariatric Surgery project,[15] which is a multicenter, prospective and comprehensive evaluation of the safety, efficacy, and mechanisms of bariatric surgery. Several cross-disciplinary funding opportunities that are supposed to bridge clinical and basic science research in obesity research, as well as ancillary studies to the Longitudinal Assessment of Bariatric Surgery project, also have been proposed in recent years. With the introduction of these projects, the National Institutes of Health appears to have recognized the need for multidisciplinary and comprehensive approaches to research in obesity and bariatric surgery. Future funding should help investigators overcome some of the challenges inherent to research in this area.

Other potentially important stakeholders in bariatric surgical research include payers and purchasers of health care. The "power of the payer" is just beginning to be harnessed in developing quality-improvement initiatives and research programs aimed at Michigan residents (BlueCross/BlueShield) undergoing bariatric surgery and Pennsylvania residents (a collaboration between a health system owned

insurer [University of Pennsylvania Medical Center Health Plan] and the providers of bariatric surgical services). There is a similar program in Washington state, which is a joint venture of commercial insurers, state purchasers of health care, and Medicaid.[16] This "power of the payer" is currently being used to fund registries of bariatric surgical care aimed at assessing quality of care, but may some day be used to address some of the more fundamental questions in the arena of bariatric surgery.

Only through a better understanding of both the mechanism of these procedures and their overall effect on patients and the health care system will physicians and the public come to appreciate the appropriate role of bariatric surgery in the care of patients with morbid obesity and those living with the complications of obesity.

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EDITORIALS

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Weighing In on Bariatric Surgery
Procedure Use, Readmission Rates, and Mortality

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In recent years, there has been a dramatic increase in the number of bariatric surgical procedures performed in the United States and worldwide.[1-4] This increase in bariatric surgery has occurred as a consequence of multiple factors. First, the increased prevalence of obesity among both children and adults in the United States has received much publicity in the medical community, media, government, and the population in general. Despite this attention and multiple calls for action at various levels, the obesity epidemic is progressive.[5] Of particular concern is the alarming increasing prevalence of obesity among children,[5] suggesting that the epidemic will worsen before it improves. Furthermore, it is estimated that at least 5% of the adult population in the United States experiences severe obesity, defined as a body mass index (BMI) greater than 40.[5]

Second, multiple epidemiologic studies have demonstrated that increasing BMI is a causative factor in many life-threatening comorbidities, including type 2 diabetes, cardiovascular disease, and cancer. Body mass index has been established as an independent risk factor for premature mortality.[6] As a result of these convincing studies, calculation of all patients' BMI as a part of their health maintenance is

See also pp 1903, 1909, and 1918.

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