

Body Composition & REE Responses to Bariatric Surgeries

PI: Dr. Dympna Gallagher

Important unanswered questions surround the nature of body composition and resting energy expenditure (REE) after substantial and sustained weight loss by severely obese persons. The LABS population is well suited for the study of these questions in that: they are of a degree of fatness rarely studied, which allows us to test and extend the range of applicability of current knowledge; they will undergo massive weight loss; the weight loss is likely to be sustained over a long period of time thereby allowing for adaptations of organ/tissue mass and fat redistribution to occur; the surgical interventions achieve their effects by different degrees of restriction and malabsorption, providing an opportunity to determine whether and how this dimension affects body composition and thermogenesis. The composition of weight loss under usual negative energy balance conditions in overweight and moderately obese persons is typically 70-80% fat and 20-30% lean tissues, however it is likely that the composition of weight loss in extremely obese persons may be different. We will analyze the composition of body weight in LABS patients undergoing rapid and large changes in weight using advanced body composition models and measurement methods. Using magnetic resonance imaging (MRI) we will describe body composition changes at the tissue/organ level and adipose tissue distribution allowing us to address questions of biological and clinical importance including the body composition changes influences on REE. The specific aims are to: 1) identify the clinically important components of weight change in persons undergoing different types of bariatric surgery on fat mass and its distribution, and on fat-free mass (FFM; including bone mineral density [BMD], skeletal muscle, and specific organs) at baseline and two time-points post surgery, and whether these are related to the type of surgery; 2) measure the change in REE following surgery induced weight loss and determine its relation to type of surgery, to changes in body composition compartments, and its duration over the follow-up. Secondary research questions relate to changes in cardiac structure and function, psychological functioning, and hormonal (ghrelin, leptin, insulin) levels associated with massive weight loss. Consenting, eligible LABS patients from Columbia University/Weill Cornell and the University of Pittsburgh will undergo some combination of the following measures: total body water by deuterium dilution (fat and FFM), extracellular water by sodium bromide tracer, body density by the BodPod, whole-body MRI (adipose tissue and its distribution; skeletal muscle mass; mass of liver, kidneys, heart, and brain), dual energy-X-ray absorptiometry (hip BMD, total body fat, FFM, and bone mineral content), and REE. Subjects will be African-American and Caucasian women and men (n=106; 50% (35>BMI kg/m²<45) will undergo MRI studies before surgery and 1 and 2 years later; 50% (45>BMI kg/m²<60) will have MRI only post surgery) equally distributed between the New York and Pittsburgh sites, and equally distributed across 3 surgical procedures: gastric banding; biliary pancreatic diversion/duodenal switch; and Roux-en-Y gastric bypass.

Psychosocial Changes After Bariatric Surgery

PI: Dr. David Sarwer

This is an initial submission by a new investigator (Dr. David Sarwer) in response to RFA DK-03-022 titled "Ancillary Studies to Obesity-Related Clinical Trials". This application is designed to serve as an ancillary study to the Bariatric Surgery Clinical Research Consortium, now referred to as Longitudinal Assessment of Bariatric Surgery (LABS). LABS is a six-center research consortium working in cooperation with NIH scientific staff to plan, develop, and conduct coordinated clinical, epidemiological, and behavioral research in bariatric surgery. This ancillary study, approved by the LABS Ancillary Study Committee, proposes to investigate changes in sexual function, sex hormones, body image, and marital functioning in 120 LABS participants and compare them with responses in 120 extremely obese individuals who do not undergo bariatric surgery.

Patients who seek bariatric surgery are often motivated to lose weight to improve their physical health. Many patients also pursue surgery and the resulting weight loss to improve their quality of life and, more specifically, their physical appearance and body image. Studies indicate that bariatric surgery confers these benefits. Few studies, however, have investigated more specific aspects of extremely obese individuals' quality of life, including sexual function. Similarly, there has been little investigation of changes in sex hormones following bariatric surgery and their potential relationship with changes in sexual function.

The LABS consortium provides an excellent opportunity to investigate long-term changes in sexual function, sex hormones, body image, and marital satisfaction in individuals who undergo bariatric surgery for extreme obesity. The proposed study will assess changes in these domains as compared to changes experienced by extremely obese individuals who do not undergo bariatric surgery. The proposed study is innovative, as it will provide new and important information on the long-term effects of bariatric surgery on these important areas of quality of life.

Physical activity and energy expenditure and gastric-bypass surgery

PI: James A Levine

Obesity is an epidemic with wide-reaching implications for health and society. Bariatric surgery is a successful therapy for achieving and maintaining weight loss and improving obesity comorbidities. This study will explore the energetic mechanisms of weight loss in subjects undergoing gastric bypass bariatric surgery, which until now has not been clearly defined.

In any scenario where there are substantial changes in energy stores, it is necessary to examine the role of changes in food intake and energy expenditure. After bariatric surgery, it is evident that energy intake declines. However, there is very little information as to how the components of energy expenditure, and in particular activity thermogenesis, change. This is not a trivial issue. In fact, changes in physical activity and activity thermogenesis could be crucial for understanding why some people lose more weight than others with bariatric surgery.

Energy balance comprises energy intake and energy expenditure. Energy expenditure includes basal metabolic rate, thermic effect of food, and activity thermogenesis. Activity thermogenesis can be further divided into exercise activity thermogenesis and non-exercise activity thermogenesis (NEAT). The latter is even more difficult to measure than the former. Most Americans, and the vast majority of those with World Health Organization Class III obesity engage in relatively little purposeful exercise, and hence the majority of energy expended in physical activity is through NEAT.

The aim of this study is to assess whether activity thermogenesis increases in patients undergoing bariatric surgery post-operatively compared to pre-operatively. We will assess non-exercise activity thermogenesis using a validated Physical Activity Monitoring System immediately pre-operatively and again at 6 months post-operatively. This is to assess activity thermogenesis and NEAT during the phase of greatest weight loss. This will permit us to address our primary hypothesis that standing/ambulation time increases six months after gastric bypass bariatric surgery compared to pre-operatively.

Overall, obesity is a major personal health and health care burden. Bariatric surgery has been shown to be beneficial without a clear understanding of the mechanism. The scientific need exists and the technology is available to uncover the role of activity thermogenesis and energy expenditure in weight loss after bariatric surgery. This may have dramatic implications for bariatric surgery and obesity management in general.

Bariatric Surgery for Morbid Obesity: Clinical and Pathophysiologic Consequences

PI: Dr. Paul Berk

Obesity is responsible for more than 300,000 deaths and \$117 billion in medical costs annually, but much of our understanding of its pathophysiology derives from studies in rodents. Bariatric surgery offers the best current treatment results in terms of weight-loss and improvement in co-morbidities such as diabetes in patients with moderate obesity, but has been a high risk procedure, with appreciable morbidity and mortality in higher obesity grades. Among obesity co-morbidities, diabetes, hypertension, dyslipidemia, arterio- sclerotic cardiovascular disease, and non-alcoholic fatty liver disease (NAFLD) have common pathogenetic mechanisms involving insulin resistance. This, in turn, relates in incompletely understood ways to the large, metabolically active, intra-abdominal fat depots typical of the "metabolic syndrome" in the obese, the movement of long chain fatty acids (LCFA) between these depots and the liver, and the "lipotoxicity" of LCFA for key non-adipose tissues, e.g. the pancreatic beta-cell. We have developed a novel two-stage laparoscopic surgical approach to high-grade obesity. A restrictive sleeve gastrectomy is followed after a ~100 lb weight loss, when the patient is a better surgical risk, by a second procedure that causes malabsorption. Our initial series of high risk patients (BMI >50) has grown to 100 cases with excellent long term weight loss, minimal morbidity, and no mortality, so that this approach has become our treatment of choice for all patients with BMI > 60 and those with BMI >50 plus other risk factors. The availability in such patients of paired biopsies of liver and of omental & subcutaneous fat at each operation will allow us to study, for the first time in man, the effects of obesity and weight loss on: [A] Key aspects of adipose tissue biology, including depot-specific effects on adipocyte LCFA uptake and lipolysis, endocrine functions of the adipocyte, and the impact of macrophage infiltration and adipokine production on these functions; [B] Patho-genetic mechanisms of NAFLD, including studies of hepatocellular LCFA and triglyceride (TG) uptake, LCFA synthesis and oxidation, lipoprotein synthesis and TG excretion; and [C] Pathogenesis of the atherogenic dyslipidemia (elevated TG, reduced HDL) of obesity. The studies will document important differences in the pathophysiology of obesity between humans and rodents, and should yield novel insights, with potential therapeutic implications, into mechanisms responsible for its key comorbidities.

Cognitive Effects of Bariatric Surgery

PI: Dr. John Gunstad

This proposal is submitted in response to RFA DK-03-022 "Ancillary Studies to Obesity-Related Clinical Trials." We are making application to prospectively examine the cognitive effects of bariatric surgery in participants from the Longitudinal Assessment of Bariatric Surgery (LABS) project.

There is growing evidence that obesity is associated with adverse neurocognitive outcome. Recent studies demonstrate that elevated body mass index (BMI) is an independent risk factor for Alzheimer's disease, structural brain abnormalities, and cognitive dysfunction in older adults. Preliminary work from our lab extends these findings and shows structural brain differences and cognitive dysfunction also exist in obese young and middle-aged adults.

Bariatric surgery is increasingly viewed as an effective intervention for morbid obesity, though its effects on cognition are unknown. Post-operative nutritional deficiencies are common and can adversely impact cognitive performance. However, substantial weight loss resolves or improves many medical conditions with reversible cognitive effects, suggesting bariatric surgery may provide cognitive benefits.

No study to date has examined the cognitive effects of bariatric surgery. To do so, the proposed study will prospectively assess cognitive performance in 125 bariatric surgery patients enrolled in the LABS project and 125 matched controls. Bariatric surgery patients will complete a computerized cognitive test battery at four time points: pre-operatively, 12 weeks post-operatively, 12 months post-operatively, and 24 months post-operatively. Matched control participants will complete the test battery at similar intervals. Demographic, medical, and psychosocial information will be collected to elucidate possible mechanisms of change.

Findings from the proposed study will provide important information regarding: 1) the cognitive effects of bariatric surgery; 2) possible mechanisms for these effects; and 3) the contribution of cognitive performance to short- and long-term outcome of bariatric surgery. Determining these effects may impart key insight into the neurocognitive consequences of obesity and identify the most effective treatment options.

Adolescent Bariatrics: Assessing Health Benefits & Risks
PI: Thomas Inge

Bariatric surgery is effective in treating extreme obesity in adults, and is most commonly used in the 5th decade. As more teenagers develop extreme obesity and seek bariatric surgery, our long term goal is to elucidate the health benefits and risks of surgical weight loss for adolescents. Our central hypothesis is that severe obesity in adolescence is associated with medical and psychosocial impairments which may be more effectively treated with surgery during adolescence rather than later in adulthood. This is based on our observations that adolescents presenting for bariatric surgery 1) have clinically occult manifestations of metabolic disease and have already developed significant health and psychosocial problems which are likely to worsen, 2) lose significant weight following bariatric surgery, and 3) experience significant improvement of a number of serious obesity-related conditions such as insulin resistance, myocardial hypertrophy, hypertriglyceridemia, and obstructive sleep apnea, depressive symptoms and quality of life. However, compliance by adolescents with prescribed medical regimens can be poor and may adversely affect beneficial outcomes of bariatric surgery performed in adolescence. Thus, the purpose of this proposal is to elucidate for the first time the benefits and define complications to be expected when bariatric surgery is performed in adolescence compared to the standard approach of performing bariatric surgery in adulthood. Our Specific Aims are: To determine whether health significantly differs between adolescents and adults seeking bariatric surgery and determine whether there is an age-related health benefit in performing bariatric surgery earlier rather than later in the lifetime; 2) To identify health risks for adolescents and adults undergoing bariatric surgery; 3) To document the psychosocial status of adolescents and adults with extreme obesity before and after bariatric surgery. Adolescents will be recruited from several high volume adolescent bariatric centers and a comparison cohort from adult bariatric centers participating in the Longitudinal Assessment of Bariatric Surgery (LABS). By comparison of key features of the metabolic syndrome, sleep apnea indices, complications, nutritional and psychosocial status, we will begin to understand medical and psychological health outcomes of bariatric surgery using obesity duration as a moderating variable. This information will be critical to scientifically inform clinical decision-making regarding appropriate timing of surgery in the life-course of Americans whose health is increasingly threatened by extreme obesity.

Melanocortine-4 Receptor Mutations and Bariatric Surgery Outcome

PI: Christian Vaisse

By building on major advances in the description of molecular pathways implicated in food intake regulation and the control of body weight, we and others have described the first gene mutations causing human obesity. The genes implicated in these monogenic forms of obesity encode proteins of the leptin axis and brain expressed targets of leptin, involved in the hypothalamic melanocortin pathway (1, 2). They include leptin (3, 4), the leptin receptor (5), proconvertase 1 (6), pro-opiomelanocortin (POMC) (7) and the Melanocortin-4 Receptor (MC4R) (8-21). Except for MC4R, mutations in these genes cause exceptionally rare, recessive, syndromic forms of obesity, associated with multiple endocrine symptoms.

MC4R is a 332 amino acid protein encoded by a single exon gene expressed at low levels in the CNS, in particular in neurons of the para-ventricular nucleus (PVN) of the hypothalamus involved in the regulation of food intake (22). Mice lacking MC4R present with a maturity onset hyperphagic obesity syndrome. MC4R belongs to the family of seven transmembrane G-protein-coupled receptors (GPCR) or serpentine receptors. MC4R transduces signal by coupling to the heterotrimeric G α s protein and activating adenylate cyclase (23, 24). Control of the level of activation of MC4R is the result of the opposing effect of the anorexigenic POMC derived melanocortin alpha-Melanocortin stimulating Hormone (α -MSH) (25) and the orexigenic antagonist Agouti related protein (AGRP). MC4R being a key integrator of different signals reflecting the metabolic status and its activation resulting in food intake inhibition, this receptor has become a major target for new anti-obesity drugs (26-28).

We initially reported the first case of human obesity linked to a mutation in the MC4R (8). In the past 5 years, we extensively studied the prevalence of MC4R mutations in both severely obese children and adults, in particular in patients undergoing bariatric surgery (2-5); we comprehensively studied the functional defects of over 50 different obesity causing MC4R mutations (11, 17-21); we further characterized the phenotype of MC4R mutation carriers and demonstrated a genotype-phenotype relationship within this disease (11, 17, 20, 29, 30).

Specific Aims

- 1) To systematically detect MC4R mutation carriers by sequencing of the MC4R gene in all participants of the LABS cohort who have provided an appropriate consent.
- 2) To systematically study the functional defect of novel detected MC4R mutations using the biochemical and cellular assays developed in our laboratory.
- 3) To determine if carriers of MC4R mutations have a different outcome after bariatric surgery than non-carriers of MC4R mutations. Within the group of patients carrying MC4R mutations, we will test for a relationship between the functional severity of the mutations and the outcome after bariatric surgery.