

University of Pittsburgh

Annual Progress Report: 2005 Nonformula Grant

Reporting Period

July 1, 2009 – May 31, 2010

Nonformula Grant Overview

The University of Pittsburgh received \$4,151,919 in nonformula funds for the grant award period June 1, 2006 through May 31, 2010. The funds are being used to support a collaborative research project entitled “*Preventing Adverse Effects of Class II and Class III Obesity.*” Accomplishments for the reporting period are described below.

Research Project: Project Title and Purpose

Preventing Adverse Effects of Class II and Class III Obesity - Severe obesity is becoming increasingly common. Increased calories and less exercise are key risk factors for becoming overweight, but why some individuals become severely obese is less clear. The first goal of this project is to examine new metabolic concepts regarding causes for severe obesity, looking at factors regulating energy metabolism and burning fat. Though moderate weight loss is recommended for overweight patients, treatment goals for severe obesity are uncertain. Severely obese participants will receive intervention to reduce weight and increase activity, and the impact on health and quality of life will be carefully examined.

Duration of Project

6/1/2006 - 5/31/2010

Project Overview

This application from the University of Pittsburgh and its partners is to establish a Center of Excellence in Research on Obesity (CERO) that will focus on severe obesity. The prevalence of severe obesity (i.e., Class II and III obesity; body mass index $> 35 \text{ kg/m}^2$ and 40 kg/m^2) is increasing more rapidly than is overweight and Class I obesity. Treatment guidelines for severe obesity are uncertain. Less than 1% of the severely obese undergo bariatric surgery, which cannot be viewed as a public health solution.

Three novel hypotheses regarding the pathogenesis of severe obesity will be tested: a) using non-invasive methods to measure energy expenditure; b) conducting an annotated lipomic search for bio-markers of impaired fat oxidation; and c) examining the role of obesity-induced inflammation as a cause for leptin resistance. Responses will also be measured following intervention with diet and activity.

Health risks of severe obesity, especially those that presage cardiovascular disease, will be comprehensively surveyed prior to and in response to intervention. Reasons for heterogeneity in health risks will be sought, examining in this context the role of race and ethnicity. Also, the impact of severe obesity on quality of life will be assessed initially and in response to treatment. These aspects of the project should lay the groundwork for evidence-based treatment guidelines for the severely obese.

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Steven Hughes, PhD - employed by Cheyney University of Pennsylvania
Stephanie Mihalik, PhD - employed by Children's Hospital of Pittsburgh
Stephen Thomas, PhD; Allan Zhao, PhD – formerly employed by Children's Hospital of Pittsburgh

Expected Research Outcomes and Benefits

There are several broad areas of anticipated benefit that will be derived as outcomes of this research conducted at the University of Pittsburgh with its partner affiliations that form the Center of Excellence in Research on Obesity. First, a better understanding will emerge as to why certain people are vulnerable to become severely obese. Tests that are relatively simple to administer, ranging from collecting breath and small blood samples, will be analyzed with state-of-the-art technology for metabolic “finger-prints” of energy expenditure, capacity to burn rather than store fat, and ability to respond to the body's cues to curb appetite.

Second, a better understanding will emerge as to how to treat severe obesity. It is commonly stated that moderate weight loss achieves major health benefits, but there is skepticism that this theory applies to severe obesity. To examine this question more carefully, thorough assessments of health will be done prior to starting a diet and activity intervention and will be repeated during the intervention. This methodology should lead to clear treatment guidelines.

Summary of Research Completed

In the fourth and final year of this project, we completed a randomized trial of diet and exercise in severely obese study participants. We completed analyses of the primary outcomes of the study in May 2010, just prior to the completion of the reporting period and the entire project. The data are presented in the abstract below, which was recently accepted to be presented in a plenary session at the annual meeting of the Obesity Society in San Diego, California in October 2010.

Title: “Nonsurgical Treatment of Severe Obesity: A Randomized Trial Examining the Effects of Diet and Physical Activity on Weight Loss and Cardiometabolic Risk Factors”

Authors: Bret H. Goodpaster, James P. DeLany, Lewis H. Kuller, Steven H. Belle, Gerald Vockley, Jeannette E. South-Paul, Stephen B. Thomas, Jolene Brown, Kathleen McTigue, Kazanna C. Hames, John M. Jakicic, Pittsburgh, PA

Apart from bariatric surgery and pharmacotherapy, few clinical trials have evaluated the treatment of severe obesity. This study determined the efficacy of a weight loss and physical activity intervention on the adverse health risks of severe obesity. One hundred-thirty participants with Class II and III obesity (15 M and 115 F, BMI = 43.6 ± 5.4 kg/m², aged 46.6 ± 6.4 years) were randomized to a one-year, intensive lifestyle intervention consisting of diet and physical activity. One group was randomized to diet and physical activity for the entire 12 months (D-PA), while the other group had the identical diet intervention but physical activity was delayed for six months (D-DPA). Attrition was 7.5% and 12.7% for D-PA and D-DPA, respectively. The intervention induced a substantial and significant ($P < 0.01$) weight loss in both groups ($-10.8 \pm 12.4\%$ for groups combined). D-PA lost significantly more weight in the first six months (-11.4 ± 0.9 vs. -8.3 ± 1.0 kg), although weight loss was not significantly different at 12 months following the introduction of physical activity in D-DPA (-12.6 ± 1.5 vs. -10.4 ± 1.5 kg). Waist circumference, visceral abdominal and hepatic fat (measured by computed tomography [CT] scan), and blood pressure were reduced in both groups. The addition of physical activity promoted greater reductions in blood pressure, abdominal fat, and hepatic fat content. In conclusion, lifestyle interventions can effectively lead to robust weight loss in the severely obese. The addition of physical activity to an intensive weight loss program results in greater weight loss and selectively greater reductions in abdominal and liver fat content as well as blood pressure.

After agreeing to present our findings at the Obesity Society meeting, we were invited by the Obesity Society and the *Journal of the American Medical Association (JAMA)* to submit our data in a research paper to *JAMA*. This primary outcomes paper is currently in review at *JAMA*. Figures 1 and 2 below highlight the key results of this trial within our Center of Excellence in Research on Obesity (CERO) project. The following abstract has also been accepted for an oral presentation to the Obesity Society:

Title: “African American Women Demonstrate Similar Adherence to Weight Loss Intervention But Lose Less Weight Due to Lower Energy Requirements”

Authors: James P. DeLany, Lewis H. Kuller, Steven H. Belle, Jeannette E. South-Paul, Stephen B. Thomas, Gerald Vockley, John M. Jakicic, Jolene Brown, Kathleen McTigue, Amy D. Otto, Kazanna C. Hames, Bret H. Goodpaster, Pittsburgh, PA

Weight loss intervention trials have shown that African American (AA) women consistently lose less weight than Caucasian (C) women. Objective measures of adherence to intervention or metabolic differences, which could explain the weight loss differences, have not been explored. We examined energy intake in severely obese women by applying the intake balance (I/B) technique; we assessed longitudinal total energy expenditure by doubly-labeled water (DLW) measurements and changes in body composition over the first six months of a lifestyle weight loss intervention trial. Prescribed energy intake was nearly identical in 24 AA and 24 C women ($1,813 \pm 161$ and $1,833 \pm 143$ kcal/d) matched for body weight (115.5 ± 16.8 vs. 115.7 ± 17.4 kg). The energy intake of AA women was nearly identical to that observed in C women ($2,608 \pm 389$ vs. $2,630 \pm 454$ kcal/d). However, AA women lost significantly less body fat (4.9 ± 3.8 vs. 7.7 ± 3.9 kg; $p < 0.02$). This lower fat loss despite similar intake could largely be explained by the lower energy requirements in the AA women over the six-month intervention (2909 ± 265 vs. 3095 ± 254 kcal/d; $p < 0.046$), resulting in a lower energy deficit (301 ± 245 vs. 464 ± 220 kcal/d). In both groups of severely obese women, the intervention was effective in achieving a decrease in energy intake; but due to significantly lower energy requirements, the AA women lost less body fat. Therefore, for AA women to achieve similar weight loss to C women, a lower energy intake would need to be prescribed when calculating caloric restriction based on body weight. Moreover, the effect of physical activity should be explored in relation to these racial differences.

The primary outcomes of our clinical trial have been analyzed and will be presented at a prominent national meeting in fall 2010. The results were recently accepted for publication in *JAMA*. In addition, we have completed data analysis for the DLW measurements of energy expenditure, which will be included in a manuscript titled “The role of energy expenditure in the etiology and treatment of severe obesity.” This manuscript will include comparisons of resting, physical (exercise and non-exercise), and total daily energy expenditure in lean, Class I, and Class II/III obesity participants and will also examine the effects of diet and diet plus physical activity on energy expenditure in the severely obese. We are also preparing another manuscript, “Impaired fatty acid oxidation in severe obesity,” in which we compare plasma acylcarnitines and whole body resting respiratory exchange ratio (RER) across lean and Class I, II, and III obese participants. In addition, we are further examining the effects of diet and diet plus physical activity on acylcarnitines and whole body RER in the severely obese.

In addition to completing a clinical trial during the project period, we completed participant enrollment and data collection for specific aim 1, which was to examine the roles of energy expenditure, impaired fatty acid oxidation, and leptin resistance in severe obesity. We enrolled a total of 132 control participants comprising normal weight ($n=30$), overweight ($n=70$), and Class I obese ($n=32$) individuals to compare cardiometabolic risk factors and inflammatory status to Class II and III obesity. We achieved our recruitment goal of 132 participants. In addition, we analyzed DLW measurements, resting metabolic rate, and data obtained from BodyMedia SenseWear™ Pro Armband activity monitors in 130 severely obese participants, as well as 48 control participants ($n=26$ normal weight and $n=22$ Class I obese).

We have presented and published six abstracts during this past year that are currently in preparation for full manuscript submission:

1. Brown JA, Hames KC, Jakicic JM, DeLany JP, Goodpaster BH: Cardiometabolic risk factors in severely obese African-American and Caucasian women. *Diabetes* 58:A630, 2009
2. Coen PM, Goodpaster BH: Circulating inflammatory monocytes (CD14+CD16+) are elevated in severe obesity. *Diabetes* 58:A356, 2010
3. DeLany JP, Vockley J, Mihalik SJ, Toledo FGS, Goodpaster BH: Increased levels of plasma acylcarnitines suggestive of dysregulation of fat oxidation in severe obesity. *Obesity (Silver Spring)* 17:S104, 2009
4. Goodpaster BH, Brown J, Hames K, Jakicic J, Chomentowski P, Zhao A, DeLany JP: Insulin resistance, fatty liver, and inflammatory markers in severely obese African-American and Caucasian women. *Obesity (Silver Spring)* 17:S125, 2009
5. Hames KC, Brown JA, Otto AD, Jakicic JM, DeLany JP, Goodpaster BH, The RSRG: Energy expenditure in severe obesity. *Medicine and Science in Sports and Exercise* 41:45, 2009
6. Brown J, Hames K, Amati F, DeLany JP, Goodpaster BH: Cardiometabolic risk and sleep duration in severely obese women. *Endocrine Reviews* 31:S502, 2010

Another objective of our project was to examine obesity-induced inflammation as a cause for leptin resistance. Leptin, c-reactive protein (CRP), and interleukin 6 (IL-6) concentrations have been measured by enzyme-linked immunosorbent assay (ELISA) in Class II and III obese participants for all baseline samples, 54 6-month samples, and 40 12-month samples. A fast protein liquid chromatography (FPLC) system purchased for the project is being used to measure serum leptin interacting proteins (SLIPs), which bind to leptin, thereby contributing to leptin resistance. We are also currently analyzing samples for levels of cytokines, insulin, and adiponectin.

Cheyney University Collaborative Project

Our objective for this collaborative project was to examine two potential mechanisms of decreased energy expenditure and decreased fat oxidation, which may explain the weight gain typically observed in both African-American and Caucasian women during the freshman year of college. During the past year, we collected data at Cheyney University and the University of Pittsburgh on resting metabolic rate and free-living energy expenditure using the DLW technique. We only recently (July 2010) obtained data from Cheyney; therefore, we are currently completing analyses of samples and data from this project.

Muscle biopsy/fatty acid oxidation substudy

During the past year, we made excellent progress in this sub-project, completing post-intervention muscle biopsies in 14 Class II/III obese participants and in 16 control participants (n=9 normal weight and n=7 Class I obese). Analyses of muscle biopsies included *ex vivo* fatty acid oxidation, mitochondrial capacity, and levels of intramyocellular lipids, including diacylglycerol and ceramides. A key finding of this study was that skeletal muscle fatty acid oxidation is impaired in severe obesity, which is in parallel with insulin resistance and elevated muscle ceramide, but not with elevated diacylglycerol content.

We also performed submaximal exercise tests in these participants to determine rates of fatty acid oxidation *in vivo*. These data revealed that Class III obese participants tend to use less energy from fat (48% of total energy from fat) compared to normal weight participants (55% of total energy from fat).

In summary, we are pleased to report that the key objectives of this project were completed during this fourth and final year and that considerable progress has been evidenced by presentations of key study findings at national meetings as well as manuscripts submitted to top medical journals. This study was the first, to our knowledge, designed specifically to examine the effects of an intensive lifestyle intervention on weight loss and other cardiometabolic risk factors in the severely obese. Our results indicate that this non-surgical approach can be an effective treatment for severe obesity.

Figure 1. Percentage body weight loss (\pm SE) for D-DPA and D-PA intervention groups at 6 and 12 months. Open symbols at 12 months represent weight loss values using intention-to-treat analysis, with the baseline observation carried forward for missing data. The star indicates significant difference in weight loss between intervention groups.

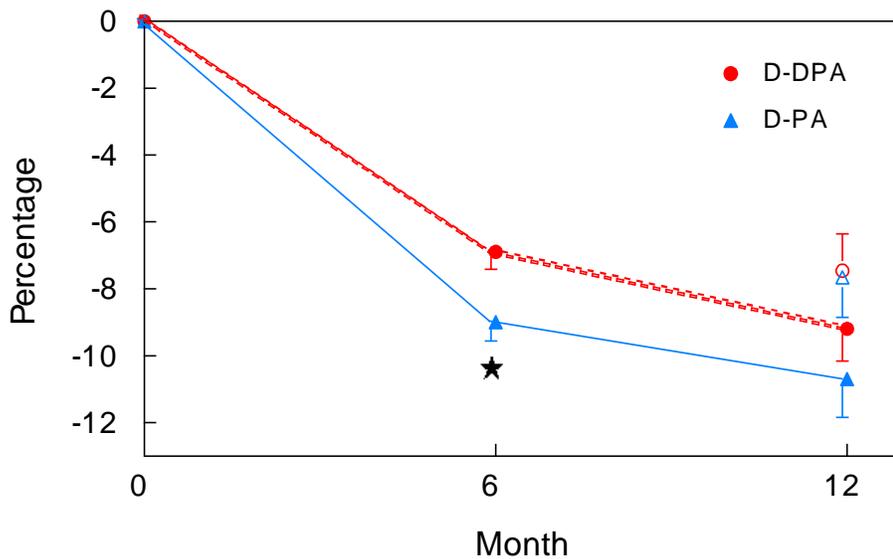


Figure 2. Percentage of participants gaining weight or losing 0-5%, 5-10%, 10-20%, or greater than 20% of body weight for the intervention groups at 6 and 12 months. The Cochran-Armitage trend test indicated a trend for higher weight loss ($p < 0.04$) in the D-PA group compared to the D-DPA group.

