Does Metabolic Adaptation To Weight Loss Occur Incrementally Or Discreetly?

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A. Study Purpose

To investigate changes in energy expenditure resulting from small increments of weight loss in non-obese subjects.

Obesity is the most common and costly nutritional problem in the United States and yet treatment towards the maintenance of weight loss is largely ineffective with recidivism rates as high as *90-95% (8).*

Body weight is tightly regulated by physiological as well as behavioral factors. A 10% reduction of body weight results in a *15%* reduction in 24-hour energy expenditure that persists in adults who have maintained a reduced body weight for *3-5* years (4). The response in lean and obese humans is identical. No significant decrease in resting energy expenditure is observed with less than a 7% decrease in body weight *(9),* and no differences in energy expenditure is observed between weight reductions of 10% and 20% below initial weight (4). This suggests that the metabolic adaptation to weight loss is triggered by either a very narrow range of weight change or by some hormonal signal, and reaches its maximal adaptive capabilities by 10% of weight loss. The narrow range of metabolic response observed, either no response or maximal, also suggest that metabolic adaptation occurs as an all-or-none phenomena instead of one of incremental change.

Leptin is a protein synthesized in and secreted by adipocytes that is postulated to serve as an afferent signal of body fat stores and may be important in modulating energy expenditure and food intake in humans *(8).*

In mice, a causal relationship between plasma leptin and energy expenditure has been established. Systemic or intracerebroventricular administration of recombinant leptin in *ob / ob* (leptin deficient) mice increases energy expenditure, lowers food intake, and decreases body weight and fat mass (1). Administration of low levels of leptin to *ob / ob* mice has an immediate effect on promoting fat over carbohydrate metabolism (2) and reversing metabolic perturbations such as hypothermia without affecting significant weight changes (1). These studies are compelling because of a potential role for leptin administration in humans to maintain reduced body weight by increasing energy expenditure and suppressing appetite.

In humans, however, the relationship between plasma leptin and energy expenditure has not been clearly established. Studies are limited by the fact that recombinant leptin has not yet been approved by the FDA for use in human subjects.

Without the ability to administer leptin, the effect of serum leptin on energy expenditure can only be observed in the context of weight loss. Since both BMI (body mass index) and fat mass are strongly correlated to energy expenditure it has been impossible to establish an independent relationship between leptin and energy expenditure.

In a study by Havel et al., the change in REE (resting energy expenditure) after a >7% weight reduction correlated significantly with plasma leptin ($r=0.40$, $P<0.02$) as well as change in BMI and percent body fat; however, partial correlation analysis did not reveal an independent relationship of any one of these variables with the change in REE. In an unpublished study by Rosenbaum, no statistically significant correlation was found between plasma leptin concentrations per unit of fat mass and measures of 24-hour energy expenditure per unit of fat free mass at usual body weight or after a 10% loss of weight (3).

Both studies, however, base correlations on only a few points of comparison, all of which represent either none or maximal adaptation of energy expenditure. By examining changes in energy expenditure and leptin over a narrower span of weight change, not only could one make observations about the mechanism of metabolic adaptation to weight change, but also, further observations can be made about the relationship between plasma leptin and energy expenditure. Like other studies designed without the ability to administer leptin to subjects, this one will not be able to draw any conclusions about the independent relationship of leptin and energy expenditure since weight change remains a confounder. It would also be informative, however, to measure energy expenditure after prolonged fasting, because it creates a situation in which leptin concentration decreases significantly (approximately 60% from baseline concentrations) without a significant decrease in body weight.(10).

The purpose of this study is two-fold:

1. To determine whether the decrease in energy expenditure is incremental or discrete (all-or-none) by examining serial measurements of resting energy expenditure during weight loss.
2. To make observations about the relationship between plasma leptin and energy expenditure, which may or may not be statistically significant.

B. Hypothesis

Within each subject, energy expenditure will either be at baseline or at a maximal adaptation. Across subjects, the threshold of metabolic change (point at which energy expenditure deviates from baseline) will be more correlated with a change in body mass index than a change in plasma leptin level. After prolonged fasting, serum leptin will decrease from baseline without a significant change of energy expenditure from baseline.

C. Methods

a. Patient Selection

i. Recruitment

Referrals from the AIM clinic and advertisements in dietary centers within the Washington Heights area.

ii. Inclusion/Exclusion

15 non-diabetic women under 60 years of age are selected. None of these women have ever been obese and are presently within 15% of ideal body weight as determined by Metropolitan Life Insurance tables. They have remained within 2 kg of present weight for the last 6 months. All subjects had normal findings on physical exams and laboratory evaluation including thyroid function tests, CBC, Chem 20, hepatitis panels, HIV antibody, glycosylated hemoglobin, and urinalysis.

b. Study Protocol

Study subjects are admitted to ICCR and after an overnight fast will undergo a series of tests: Resting energy expenditure will be measured by indirect calorimetry at 7AM before rising, with a Beckman MMC Horizon metabolic cart fitted with a ventilated hood. Plasma leptin will be determined from samples drawn after overnight fast. Samples will be centrifuged and frozen and will be measured by solid-phase sandwich enzyme immunoassay in the ICCR Core Lab. Body composition will be analyzed by hydrodensitometry and all subject will be weighed with a standardized scale.

After completion of the studies at initial weight, 10 subjects are fed 800 kcal of the dietary formula liquid formula (40% fat from corn oil, 45% carbohydrate from glucose polymer, and 15% protein from casein hydrolysate, supplemented with 5.0 g iodized NaCl, 1.9 g of KCI, and 2.5 g calcium carbonate per day, 1 mg of folic acid twice weekly and 36 ng of ferrous iron every other day) per day until their body weight has been reduced 10% below their initial weight. This will occur within a 4-6 week period.

These 10 subjects will be weighed daily and have the above series of measurements performed every 4 days (resting energy expenditure, fasting plasma leptin, and body composition assessment). Once a 10% weight decrease has been achieved, a final set measurements will be made on the next scheduled day in the 4 day cycle.

After the initial measurements, 5 subjects will undergo a 72 hour fast during which only water and herbal tea are allowed without restriction. Adherence to fast will be verified by determinations of plasma glucose, insulin, and first void urinary ketones. Serum leptin will be drawn every 24 hours at 7 am. After 72 hours, resting energy expenditure, plasma leptin and body composition will be measured as above. Subjects are then allowed to have an unrestricted diet. On the following morning, after an overnight fast, subjects will have resting energy expenditure, plasma leptin and body composition measured as stated above.

c. Analyses

Each subject's energy expenditure and leptin will be plotted against weight. At the point of departure from baseline resting energy expenditure, Serum leptin concentration, change in leptin, Body mass index, change in BMI will be expressed as mean +/- SD for all subjects.

D. Risks and Benefits

Very little risks are involved. Subjects will be monitored throughout process of weight loss by competent Columbia Presbyterian house-staff and win be given a follow-up visit 3 months after the termination of study.

Aside from the benefits of contributing to the research of obesity, one additional benefit is that subjects who desire to lose weight for purposes of health and cosmetics have an opportunity to lose weight in a monitored setting with a nutritionally balanced diet regimen. They will also have the opportunity to participate in regular classes run by nutritionist as part of their hospital stay. Furthermore, they will receive monetary compensation of $100 per week given every Saturday with a bonus of $100 per week if they complete the estimated 6 week study. Fasting subjects will receive a flat compensation of $200 at the end of their testing.

E. References

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