The Effects of Moderate Caloric Restriction on Body Weight and Serum Lipids in Healthy Overweight Humans

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A. Study Purpose and Rationale

For over a century, physicians have recommended lifestyle interventions like prudent diet and moderate exercise to maintain health and normal body weight[1]. Large scale epidemiological data in both healthy and chronically ill individuals have consistently supported this assertion[2,3,11]. Over 60 years ago, McKay observed the ability of total caloric restriction (CR) to extend murine lifespan[4,5]. Subsequently, there have been studies demonstrating that CR in animals may result in decreased mutagenesis[10] resulting in an active search for a potential molecular mechanism for this effect. Other investigators have begun to investigate if CR can increase lifespan in non-human primates[8].

The progress in elucidating similar effects in humans has been slower. An initial study in 32 subjects restricted caloric intake to 50% of what is needed to maintain ideal body weight (IBW). This severe diet, which did not supply critical micronutrients, resulted in severe weight loss and deterioration of physical and mental performance[6]. A second 3 month feasibility study in 16 experimental and 8 control subjects, restricted total caloric intake to 80% of intake for IBW. While both physical and mental performance were not significantly altered in experimental subjects, there was a significant decrease in weight and an increase in HDL cholesterol[7]. The implications were that moderate CR in humans could be done safely while potentially affecting risk factors for chronic disease.

The potential for human benefit in this area of research is promising. Healthy lifestyle interventions that emphasize active patient involvement, while difficult for some, allow individuals far greater "ownership" over their health care decisions, offer greater opportunity for sustainability and are able to change multiple risk factor profiles.

Because it is difficult to demonstrate CRs potential effect of extended lifespan and decreased mutagenesis in humans in a non-epidemiologic controlled setting, there remains the question of what effect can CR have on modification of known risk factors for chronic disease. This study will attempt to examine short term CR effects on weight, total cholesterol and its subfractions and thus a potential effect on future coronary heart disease morbidity.

B. Study Design and Statistical Analysis

The study will be a randomized double blinded placebo controlled design. Subjects will be healthy sedentary mildly dyslipidemic overweight individuals. Control subjects will complete a 12 week Step I NCEP diet at a caloric intake sufficient to maintain IBW. The interventional group will complete an identical diet with equal macronutrient composition but at 80% of calculated total caloric intake. There will be a total of 40 subjects. This was determined by the highest calculated number for an unpaired paired t test with 80% power testing at p=0.05 to detect a change of 3 kg (+/-2) of body weight, 8 mg/dl (+/-6) of total cholesterol, 5 mg/dl (+/- 1) LDL cholesterol, 3 mg/dl (+/-1) of HDL cholesterol and 4 mg/dl (+/-3) of triglycerides. To detect the mean change from baseline between the two groups, an unpaired t-test for total cholesterol, HDL, LDL, triglycerides and weight will be performed.

C. Study Procedure

At the outset of the study, subjects will be weighed on three subsequent days and an average of the three will be recorded. Fasting glucose and lipid panel will be measured after a 12 hour fast on subsequent days. An average of the two measurements will be recorded. This Harris-Benedict Equation

will calculate the amount of daily calories sufficient to maintain IBW. Subjects will eat only food that is prepared as part of the study. They will receive all food from a designated kitchen at CPMC that is experienced in the preparation of food for diet studies[9]. All subjects will receive vitamin supplementation. Subjects will be asked not to alter their exercise habits. Dinner will be eaten at the study site every evening except on weekends, where on Friday, a supply of two full days will be distributed. Both breakfast, lunch, and snacks will be provided for the following day at the time of the daily pickup. For all subjects, there will be one visit each month with a study coordinator to assess for any serious complication. If present, the coordinator will refer the subject to his or her PMD who can evaluate whether continuing the study poses a great risk to the patient. At the completion of the study, weight will be recorded on three subsequent days and an average of the three will be recorded. Morning fasting cholesterol panel analysis will be performed twice daily after the final day of the study period. An average of the two values will be recorded. We will use a standard commercial enzymatic assay for cholesterol, HDL, trigylcerides. LDL will be calculated using the Friedwald formula (total cholesterol – [hdl – (trig/5)].

D. Study Drugs

Not applicable

E. Medical Device

Not applicable

F. Study Questionnaires

Not applicable

G. Study Subjects

Inclusion/Exclusion criteria:

Healthy non-smokers, normotensive (SPB <140, DBP <90) mildly dyslipidemic (hdl <50, LDL 100-190, TG 30-300, measured after a 12 hour fast,) men and non-pregnant, clinically pre-menopausal women of any ethnic group age 35-50 with a BMI of 25-30 (height in m^2/wt in kg). Patients will not be on any chronic medication, or have any family history of early cardiac disease. Subjects will be excluded if their fasting glucose is 126.

H. Recruitment of Subjects

Subjects will be recruited through the AIM clinics, Atchley private clinics, and advertisements throughout the Columbia Presbyterian Medical Center. All patients recruited through the clinics will have their primary M.D. agree that the patient is suitable for the study.

I. Confidentiality of Study Data

All patients will receive a unique study code number which will be used to track their involvement in the study, including personal data, blood work, and weights.

J. Potential Conflict of Interest

The investigators of this study have no proprietary interest in a calorie restriction diet and will not benefit financially in any way from the results of this data.

K. Location of the Study

The study will take place at Columbia Presbyterian Medical Center. All weights and blood work will be drawn at the GCRC. Meals will be provided at the GCRC.

L. Potential Risks

Potential risks to the study participants include excessive weight loss from restricted calorie intake, though as these patients are already clinically overweight, the risk in a 3 month study at only 20% restriction is minimized. For example, an individual who requires 2400 Kcal/d on a weight maintenance diet will receive approximately 500 kcal fewer per day on an 80% CR diet. With stable activity expenditure, this amounts to a weight loss of only 1 lb. per week. Micronutrient intake is a theoretic risk but should be minimized by provision of multi-vitamins for all participants. Abdominal discomfort, poor concentration, fatigue, and decreased energy are all potential risks of CR though this effect is more likely at more severe levels of energy restriction.

M. Potential Benefits

For overweight, hypercholesterolemic subjects, CR may provide an effective low cost safe option for weight reduction and cholesterol lowering. Potential benefits to society include a cost-effective population based option for weight reduction and its subsequent risk factors for chronic disease.

N. Alternative Therapies

Prudent diet and exercise remain the standard of care for all overweight individuals. Alternative therapies already available to subjects for management of mild hypercholesterolemia include low fat diet in conjunction with exercise. Drug therapy for otherwise healthy patients is usually deferred until a trial of lifestyle intervention has been ineffective. The alternative therapies for weight loss in overweight individuals include pharmacotherapy with its own inherent risks of vitamin deficiency, drug toxicity, and cardiac effects. Gastric bypass is usually reserved for those obese subjects refractory to conservative management.

O. Compensation to Subjects

At the completion of the study, all subjects will be paid $400 by check to cover costs of transportation and time.

P. Costs to Subjects

The only costs patients will incur are those of time and transportation to the study center.

Q. Minors as Research Subjects

Not Applicable

R. Radiation or Radioactive Substances

Not Applicable

S. References:

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