

CALORIC RESTRICTION AND HUMAN METABOLISM

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Introduction: Caloric restriction (CR) is the only mechanism known to extend life span and retard age-related chronic diseases. This has been proven repeatedly in a variety of species including rats, mice, fish, flies, worms and yeast. CR reduces metabolic rate and oxidative stress, improves insulin sensitivity and stress response, and alters neuroendocrine and sympathetic nervous system function. Whether any, or all of, these changes provide the mechanism for life-span extension effect is presently unresolved. Furthermore, the effects of prolonged CR on biomarkers of aging in non-obese humans are unknown. In experiments of nature, humans have been subjected to periods of non-volitional partial starvation. However, in almost all of these cases the diets have been of poor quality. The absence of adequate information on the effects of good quality CR diets in non-obese humans reflects the difficulties involved in conducting long-term studies in an environment so conducive to overfeeding. CALERIE (Comprehensive Assessment of Long-Term Effects of Reducing Intake of Energy funded by the National Institute on Aging) was designed to determine if prolonged caloric restriction (CR) improves biomarkers of aging and chronic diseases (such as cardiovascular disease and type 2 diabetes) in non-obese humans.

Study design at Pennington: Following extensive screening procedures, 48 healthy, non-smoking male (25-50y) and female (25-45y), overweight participants ($25 \leq \text{BMI} \leq 30$) were enrolled in a 6-month intervention. Subjects completed two 2-week baseline measures of total energy expenditure by doubly labeled water (DLW) and other metabolic tests before they were randomized to one of four interventions; 1) 25% CR of baseline calories required to maintain weight, 2) combination of increased physical activity (12.5%) and CR (12.5%), 3) very low calorie diet until 15% weight loss is achieved, followed by weight clamping at the new lower body weight, and 4) control group. Metabolic tests that were conducted at baseline and at 3-month intervals included; body composition by DXA, computed tomography and magnetic resonance spectroscopy; metabolic rate under resting conditions by a ventilated hood system, over 24h in a metabolic chamber and in free living conditions by DLW; core temperature; endothelial function and other traditional markers for CVD; markers for oxidative stress including lipid peroxidation, protein carbonylation, and DNA damage; insulin secretion and sensitivity by the minimal model; neuroendocrine function by measuring the diurnal rhythm of leptin, growth hormone pulsatility and salivary cortisol. Skeletal muscle and adipose tissue biopsies were taken to assess numerous genes involved in longevity, oxidative stress and energy metabolism. **Hypothesis:** We are testing the hypothesis that CR will reduce metabolic rate out of proportion with the reduction in fat-free mass and decrease oxidative damage to DNA, protein and lipids. We also hypothesize that CR will improve insulin sensitivity and the cardiovascular profile, including endothelial function and that CR will reduce the activity of the sympathetic nervous system and modulate the activity of neuroendocrine axes via a decrease in leptin production. 46 of the 48 subjects completed the intervention and selected preliminary findings will be discussed. Specifically, the results on energy expenditure, oxidative stress, neuroendocrine function, and skeletal muscle candidate gene expression will be used to highlight the value of the human system for the conduct of mechanistic studies that are difficult to perform in rodents and other model systems.