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Caloric restriction alone and with exercise improves CVD risk in healthy non-obese individuals

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Abstract

Calorie restriction (CR) delays the development of age-associated disease and increases lifespan in rodents, but the effects in humans remain uncertain.

Purpose: Determine the effect of 6 months of CR with or without exercise on cardiovascular disease (CVD) risk factors and estimated 10-year CVD risk in healthy non-obese men and women.

Methods: Thirty-six individuals were randomized to one of three groups for 6 months: Control, 100% of energy requirements; CR, 25% calorie restriction; CR + EX, 12.5% CR + 12.5% increase in energy expenditure via aerobic exercise. CVD risk factors were assessed at baseline, 3 and 6 months.

Results: After 6 months, CR and CR + EX lost approximately 10% of body weight. CR significantly reduced triacylglycerol (-31 ± 15 mg/dL) and factor VIIc ($-10.7 \pm 2.3\%$). Similarly CR + EX reduced triacylglycerol (-22 ± 8 mg/dL) and additionally reduced LDL-C (-16.0 ± 5.1 mg/dL) and DBP (-4.0 ± 2.1 mmHg). In contrast, both triacylglycerol (24 ± 14 mg/dL) and factor VIIc ($7.9 \pm 2.3\%$) were increased in the Control group. HDL-cholesterol was increased in all groups while hsCRP was lower in the Controls versus CR + EX. Estimated 10-year CVD risk significantly declined from baseline by 29% in CR ($P < 0.001$) and 38% in the CR + EX ($P < 0.001$) while remaining unchanged in the Control group.

Conclusions: Based on combined favorable changes in lipid and blood pressure, caloric restriction with or without exercise that induces weight loss favorably reduces risk for CVD even in already healthy non-obese individuals.

Keywords: Caloric restriction; Exercise; Cardiovascular risk factors; Nutritional intervention; Weight loss; Aging

1. Introduction

Prolonged caloric restriction (CR) has been suggested as an anti-aging strategy in the belief that it will extend lifespan and improve quality of life. While data are convincing in shorter-lived species [1], whether calorie restriction extends lifespan in humans is not known. Heart disease and stroke are the number one and three causes of death in the USA [2], hence delaying the progression of atherosclerotic cardiovascular disease maybe one potential mechanism by which CR promotes longevity. The risk factors for CVD including blood lipids, blood pressure, hemostatic factors, inflammatory markers and endothelial function are all

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worsened with aging [3–6]. At least a portion of these age-related changes appear to be secondary to increases in adiposity and/or reductions in physical activity [7,8] and, therefore, may be amenable to improvements through prolonged caloric restriction and/or increased physical activity.

It is well established that obesity is associated with increased CVD mortality [9] and weight loss in obese individuals by CR is associated with improvements in CVD risk factors [10] and a lowering of coronary heart disease event rates [11]. Increased physical activity, primarily through aerobic exercise also reduces the risk for atherosclerotic disease, acute cardiovascular events, stroke and Type 2 diabetes mellitus [12,13]. Thus, it would be expected that increasing physical activity as a means to achieve a negative energy balance in conjunction with CR would provide benefits at least equivalent (or superior) to that of simply reducing caloric intake.

The Comprehensive Assessment of the Long Term Effects of Reducing Intake of Energy (CALERIE) study examined the potential health benefits of CR in sedentary, non-obese, healthy individuals. While the primary aim of the study was to determine the impact of CR on biomarkers of longevity and metabolic adaptation [14] the secondary aims were to evaluate the changes in risk factors for type 2 diabetes mellitus [15] and CVD. We hypothesized that 6 months of CR would improve markers for CVD and that changes in CVD risk factors would be similar whether the energy deficit was produced by combining exercise with CR or by CR alone.

2. Methods

2.1. Study participants

Forty-eight healthy, non-smoking male (25–50 years) and female (25–45 years), overweight participants ($25 \leq \text{BMI} < 30$) were recruited to participate in a 6-month intervention [14]. Participants were excluded if they had a history of CVD, elevated blood pressure (>160/90 mmHg), high fasting blood glucose (>126 mg/dL), chronic medications (except oral contraceptives), smoking, regular exercise (more than twice a week), abnormal thyroid function or abnormal ECG. The study was approved by the Pennington Center Institutional Review Board and the CALERIE Data Safety Monitoring Board. All subjects provided written informed consent.

2.2. Study design

Participants were randomized into one of four groups for 24 weeks: Control = healthy weight maintenance diet, CR = 25% caloric restriction from baseline energy requirements, CR + EX = 12.5% caloric restriction and 12.5% increase in energy expenditure through structured aerobic exercise and LCD = low calorie diet (890 kcal/day) to rapidly achieve 15% weight loss. Because of the different rate and extent of weight loss (rapid over 3 months) and different macronutrient composition, we did not include the LCD group in this analysis. Study outcomes were assessed during a 5-day inpatient stay at baseline and during weeks 12 (M3) and 24 (M6) of intervention.

2.3. Energy prescription

Individual values used to prescribe the daily energy content during the intervention were calculated at baseline from total daily energy expenditure assessed during two 14-day periods by doubly labeled water and changes in body weight during a 2-week period when participants consumed all meals prepared by our metabolic kitchen [14].

2.4. Diets and diet delivery

All diets were based on the American Heart Association guidelines; 30% fat, 15% protein and 55% carbohydrate and provided the RDA for all essential vitamins and minerals. During weeks 1–12 and 23–24 of the intervention, participants consumed only foods prepared by our metabolic kitchen. During weeks 13–22 participants self-selected a diet based on their individual calorie target. Multivitamin and mineral supplements (including calcium) were not permitted.

2.5. Exercise

Except for participants in CR + EX, other participants were not permitted to modify their physical activity pattern. The CR + EX group increased their energy expenditure by 12.5% above baseline by undergoing supervised aerobic exercise, 5 days/week. The exercise time necessary to expend the 12.5% calorie target was determined for each individual by indirect calorimetry (V-max, Sensormedics, Yorba Linda, CA) and exercise sessions were monitored by heart rate (Polar S-610, Polar Beat, Port Washington, NY) [14]. Participants self-selected their exercise intensity which ranged from 47 to 76% VO_{2max} (women: 47–70% VO_{2max} and men: 48–76% VO_{2max}). The energy expenditure target for the exercise intervention was 403 ± 63 kcal per session for women and 569 ± 118 kcal for men per session which at the self-selected exercise intensity represented 53 ± 11 and 45 ± 14 min per session for women and men, respectively.

2.6. Behavioral intervention

Commencing at baseline, participants attended weekly meetings to teach subjects how to adhere to their meal and exercise plans and to boost motivation and morale. Emphasis was placed on teaching participants the skills necessary to modify eating behavior and comply with the interventions during the out-patient phase of the study.