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Effect of Caloric Restriction in Non-Obese Humans on Physiological, Psychological and Behavioral Outcomes

Leanne M. Redman, Corby K. Martin, Donald A. Williamson, and Eric Ravussin

Pennington Biomedical Research Center, 6400 Perkins Road, Baton Rouge, LA, 70808

Abstract

The focus of this review is on current research involving long-term calorie restriction (CR) and the resulting changes observed in physiological and behavioral outcomes in humans. Special emphasis will be given to the first completed clinical studies which are currently investigating the effects of controlled, high-quality energy-restricted diets on both biomarkers of longevity and on the development of chronic diseases related to age in humans. Prolonged CR has been shown to extend both the median and maximal lifespan in a variety of lower species such as yeast, worms, fish, rats, and mice. Mechanisms of this CR-mediated lifespan extension are not fully elucidated, but possibly involve significant alterations in energy metabolism, oxidative damage, insulin sensitivity, and functional changes in both the neuroendocrine and sympathetic nervous systems. In this brief report, we review some of the major physiological, psychological and behavioral changes after 6 month of CR in overweight otherwise healthy volunteers. Ongoing studies of prolonged CR in humans are now making it possible to analyze changes in “biomarkers of longevity” to unravel some of the mechanisms of its anti-aging phenomenon. With the incremental expansion of research endeavors in the area of energy or calorie restriction, data on the effects of CR in animal models and human subjects are becoming more accessible. Detailed analyses from controlled human trials involving long-term CR will allow investigators to link observed alterations from body composition down to changes in molecular pathways and gene expression, with their possible effects on the biomarkers of aging.

Keywords

calorie restriction; longevity; metabolic adaptation; quality of life; physical activity

Why Caloric Restriction?

Calorie restriction (CR), a dietary intervention that is low in calories but maintains proper nutrition, is the only intervention known to date that consistently decreases the biological rate of aging and increases both average and maximal lifespan. Since the first report of prolonged lifespan in rodents more than 70 years ago [1] similar observations have been reported across a wide range of species including yeast, worms, spiders, flies, fish, mice and rats [2]. While the effects of CR in longer lived species remains unknown, results reported thus far from 3 nonhuman primate colonies suggest that CR might have a similar effect in longer-lived species. While lifespan data remains inconclusive [3], CR monkeys display a substantially reduced age-

Tel. 1-225-763-3186, Fax. 1-225-763-3030, Email. ravusse@pbrc.edu.

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related morbidity [4,5]. In humans, data from controlled trials is lacking and of course no long-term prospective trials of CR have been conducted with survival being the primary end-point [6]. There is however, a lot that can be learned from a handful of epidemiological and cross-sectional observations in longer-lived humans, centenarians and individuals who self-impose CR.

Centenarians from Okinawa

Probably the most intriguing epidemiological evidence supporting the role of CR in lifespan extension in humans comes from the Okinawans [7]. Compared to most industrialized countries, Okinawa, Japan has 4–5 times the average number of centenarians with an estimated 50 in every 100,000 people [8]. Reports from the Japanese Ministry of Health, Labor and Welfare show that both the average (50th percentile) and maximum (99th percentile) lifespan are increased in Okinawans. From age 65, the expected lifespan in Okinawa is 24.1y for women and 18.5y for men compared to 19.3y for women and 16.2y for men in the USA [9]. What is interesting about this population is that a low caloric intake was reported in school children on the island more than 40 years ago and later studies confirmed a 20% CR in adults residing on Okinawa compared to mainland Japan [10]. Importantly, reports indicate that the diets which were typically rich in green leafy vegetables, soy and some fish were similar with CR interventions providing adequate amounts of nutrients, essential vitamins and minerals [9].

The Valjejo study

To our knowledge there is only one study that was designed to test the effects of CR without malnutrition in non-obese humans [11]. This was a study of alternate day feeding in 120 men whereby the 60 participants in the CR group received an average of 1500 kcal per day for 3 years whereas the 60 others were *ad libitum*. This amounted to approximately 35% CR compared to the control group. While the initial report was brief, post-hoc analyses conducted several years later [12] indicated that death rate tended to be lowered in the CR group and hospital admissions were reduced in these individuals by approximately 50% (123 days for CR vs. 219 days for Control).

Randomized controlled trials of calorie restriction in non-obese humans

As for randomized controlled trials, results from a 2 year study of CR in humans is only a few years away. The National Institute on Aging (NIA) is sponsoring a trial; CALERIE (Comprehensive Assessment of the Long-term Effect of Reducing Intake of Energy) which is for the first time, scientifically testing the effects of 25% CR in ~150 non-obese healthy men and women aged 25–45y. Three clinical sites are involved in the trial; Washington University in St. Louis, MO, Tufts University in Boston, MA and the Pennington Biomedical Research Center in Baton Rouge, LA. The protocol and endpoints for this multi-center trial were developed from 3 independent Phase 1 trials conducted at each clinical site [6,13,14].

The focus of this review will be the results from the Phase 1 study conducted at the Pennington Center. For six months, 48 men and women were randomized to one of four treatment groups [15–23]. For the CR group, individuals were restricted to 75% (a 25% CR) of their weight maintenance energy requirements. The other groups were: 1) CR plus exercise group for which the calorie deficit was also 25% from weight maintenance but half (12.5%) was achieved by CR and half (12.5%) by increasing energy expenditure with structured aerobic exercise, 2) a low calorie diet group in which participants consumed 890 kcal/d to achieve a 15% weight loss and thereafter followed a weight maintenance diet and 3) a healthy diet control group that followed a weight maintaining diet based on the American Heart Association Step 1 diet. The effects of the calorie restriction interventions were determined from changes in various physiological and psychological endpoints after three and six months.

Physiological Effects of Caloric Restriction

Aging is considered to be either ‘primary’, that is the inevitable deterioration of cells and tissues structure and function that occurs independent of disease, lifestyle and environmental causes or, ‘secondary’ where the decline in tissue structure and function occurs as a result of external influences including diseases [24]. Attenuation of primary aging therefore results in an increase in maximal lifespan, whereas delays in the progression of age-related disease or secondary aging increases mostly mean lifespan. Calorie restriction (CR) is the only known non-pharmacological intervention that can slow primary aging and also has a protective effect against secondary aging. Six months of CR produced favorable alterations in physiological and behavioral outcomes (Table 1). Results from the first randomized study of calorie restriction (CALERIE) at the Pennington Center are discussed below:

a. Body composition

Throughout the six month intervention there was a progressive decline in body weight that reached ~10% for the CR group at the completion of the study [15]. Body composition analysis by dual x-ray absorptiometry and multi-slice computed tomography showed that the loss of tissue mass was attributable to significant reductions in both fat mass (CR: $-24 \pm 3\%$) and fat-free mass (CR: $-4 \pm 1\%$), and a 27% decrease in both visceral and subcutaneous fat depots. It was interesting to note that the fat distribution within the abdomen was not altered by CR [15]. We also observed a reduction in subcutaneous abdominal mean fat cell size by ~20%, a lowering of hepatic lipid by ~37% but no change in skeletal muscle lipid content [21].

b. Biomarkers of longevity

A “biomarker of aging” is considered to be any parameter that reflects physiological or functional age; it must undergo significant age-related changes, be slowed or reversed by treatments that increase longevity (e.g. calorie restriction), and must be reliably measured (Figure 1). Numerous biomarkers have been identified in rodents and primates including temperature and hormones DHEA-S and insulin [25]. In the CALERIE study, 2 out of the 3 biomarkers of longevity [25] were improved with six months of 25% CR [6]. Significant reductions were observed in both fasting insulin concentrations ($-29 \pm 6\%$) and core body temperature ($-0.20 \pm 0.05^\circ\text{C}$), whereas DHEA-S was unchanged by the intervention (Figure 2). These findings of course echo results previously reported in nonhuman primates and rodents on CR and long lived men in The Baltimore Longitudinal Study of Aging [25].

c. Diabetes and Cardiovascular risk factors

With heart disease and stroke ranked numbers one and three in the causes of death in the USA [26] 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 worsened with aging [27,28]. At least a portion of these age-related changes appear to be secondary to increases in adiposity and/or reductions in physical activity [29,30] and, therefore, may be amenable to improvements through prolonged caloric restriction. Six months CR significantly reduced triacylglycerol (TG) and factor VIIc by 18% and 11%, respectively. HDL-cholesterol was increased and fibrinogen, homocysteine and endothelial function were not changed. According to total and HDL cholesterol (expressed as their ratio), systolic blood pressure, age and gender, estimated 10-year CVD risk was 28% lower after only six months of CR.

Insulin resistance is an early metabolic abnormality that precedes the development of hyperglycemia, hyperlipidemia and overt type 2 diabetes. Both insulin resistance and β -cell dysfunction are associated with obesity [31–33]. Calorie restriction reduces fat mass and delays

the development of age-associated diseases such as type 2 diabetes. While in obese humans, it is well established that calorie restriction and weight loss improve insulin sensitivity [34, 35], the effects of calorie restriction on insulin sensitivity and therefore diabetes risk is not well understood in overweight and lean individuals. In our study of six months CR we observed a 40% improvement in insulin sensitivity in the CR group, although this did not reach significance ($p=0.08$) [21]. The acute insulin response to glucose (AIRg), however was significantly decreased from baseline (CR: $29\pm 7\%$, $p<0.01$) indicating an improvement in β -cell responsiveness to glucose.

d. Metabolic Adaptation and Oxidative Stress

One of the most popular proposed theories by which CR promotes lifespan extension is the rate of living theory [36]. It is hypothesized that a lowering of the metabolic rate (rate of living) reduces the flux of energy with a consequential lowering of reactive oxygen species and rate of oxidative damage to vital tissues [37]. Indeed, CR is associated with a robust decrease in energy metabolism, including a lowering of resting metabolic rate (or sleeping metabolic rate), lowering of the thermic effect of meals and a decrease in the energy cost of physical activity. However, whether total energy expenditure is reduced beyond the expected level (i.e. metabolic adaptation) for the reduction in the metabolizing mass (fat-free and fat mass: FFM and FM) following CR is debated.

Absolute 24-h energy expenditure and sleeping metabolic rate (both measured in a respiratory chamber) were significantly reduced from baseline with CR ($p<0.001$) as expected for the loss of body mass. Importantly both 24-hour sedentary and sleeping energy expenditures were reduced ~6% beyond what was expected for the loss of metabolic mass (i.e. FFM and FM) [6]. This metabolic adaptation was also observed in RMR measured by a ventilated hood indirect calorimeter [16]. These physiological responses were associated with a reduced amount of oxidative stress as measured by DNA damage. DNA damage was reduced from baseline after six months in CR ($p=0.0005$), but not in controls. In addition 8-oxo7,8-dihydro-2'-deoxyguanosine (8oxodG) was also significantly reduced from baseline in CR ($p<0.0001$). These data confirm findings in animals that CR reduces energy metabolism, oxidative stress to DNA, both potentially attenuating the aging process.

e. Endocrine Adaptations

Thyroid function—Short-term studies of CR in humans have reported alterations in thyroid function. Four weeks of complete fasting resulted in a decrease in triiodothyronine (T3) and increase in reverse triiodothyronine (rT3) which was associated to a reduction in metabolic rate [38]. The CRONIES (a self selected group engaging on long-term CR) have significantly lower T3 but not thyroxine (T4) or thyroid stimulating hormone (TSH) concentrations compared to age-, sex- and weight-matched controls [39]. In the CALERIE study, plasma T3 concentrations were reduced from baseline in the CR group after 3 ($p<0.01$) and 6 months ($p<0.02$) of intervention [6]. Similar results were found for change in plasma T4 in response to the treatment. When the data of the subjects in the three CR groups were combined into one intervention sample, we observed significant linear relationships between the change in plasma thyroid hormones and the degree of metabolic adaptation in 24-h sedentary energy expenditure at month 3 of intervention (T3; $r=0.40$, $p=0.006$ and T4; $r=0.29$, $p=0.05$) [6].

The Somatotrophic Axis—Aging is marked by a reduction in both growth hormone (GH) and insulin like growth factor-1 (IGF-1) concentrations in healthy adults resulting from a reduced amount of GH secreted at each burst without alterations of burst frequency or GH half life [40]. Unlike rodents, weight loss via energy restriction in humans increases GH [41]. After six months of CR, 11-hour mean GH concentrations were not changed with CR nor was the secretory dynamics in terms of the number of secretion events, secretion amplitude and

secretion mass (unpublished data). The fasting plasma concentration of ghrelin, a GH secretagogue was significantly increased from baseline but IGF-1 was unaffected. Despite a significant reduction in weight and visceral fat and an improvement in insulin sensitivity, mean GH concentrations were not altered by the six month intervention. In agreement with this observation was the finding that both GH and IGF-1 were not affected by the chronic food shortage experienced by the individuals in Biosphere 2 [42].

f. Physical Activity

Daily energy expenditure has three major components: resting metabolic rate (RMR), the thermic effect of food and the energy cost of physical activity. Investigation of changes in physical activity are important in studies of CR not only because the contribution of physical activity to daily energy expenditure is variable, but also because it is not known if individuals volitionally or non-volitionally decrease their level of physical activity in an attempt to conserve energy [43]. In our study of 25% CR in overweight humans, we observed no change in spontaneous physical activity in a respiratory chamber [16] consistent with earlier reports of no alterations in spontaneous physical activity [44] or posture allocation in obese individuals following weight loss [45]. These findings are not surprising if the current hypothesis that spontaneous physical activity is biologically determined is true [45,46].

However with a measure of energy metabolism in free-living conditions (total daily energy expenditure by doubly labeled water) we found that a metabolic adaptation exists after three months (-386 ± 69 kcal/d) but not after six months of CR (unpublished data). This adaptation was evident even after total daily energy expenditure (TDEE) was adjusted for sedentary energy metabolism (24-h or sleeping energy expenditure) indicating that changes in other components of daily energy expenditure such as physical activity and diet-induced thermogenesis are also involved. In support of this, physical activity level calculated by either the ratios of TDEE to RMR or sleeping metabolic rate [16], or TDEE adjusted for sleeping metabolic rate, was significantly reduced at month three by 12% and returned toward baseline values after six months of intervention. Interestingly, despite lower physical activity levels, participants reported an improvement in physical functioning, a primary component of quality of life. All the effects of caloric restriction on physiological outcomes are summarized in Table 1.

Psychological and Behavioral Effects of Caloric Restriction

Calorie restriction in humans might prove to have positive effects on physical health and longevity, resulting in the practice of CR or the identification of CR mimetics. If people attempt to follow CR for health promotion, important questions must be answered about possible negative effects of CR on psychological well-being, cognitive functioning, mood, and subjective feelings of appetite. Determining the effect of CR on these parameters is critical to learn if adhering to a CR regimen is feasible and if CR has unintended negative consequences that would offset the potential health benefits of CR. Phase I of CALERIE provided a unique opportunity to examine the effect of six months of CR on psychological and behavioral endpoints in a randomized controlled trial. We here summarize the effects of CR on the development of eating disorder symptoms, quality of life, mood (symptoms of depression), subjective ratings of appetite, and cognitive function (Table 1).

a. Development of Eating Disorder Symptoms

One of the most pressing concerns about CR is the potential development of eating disorder symptoms. This concern is based in part on the Keys [43] study, which found that 50% CR for six months among healthy men was associated with the development of eating disorder symptoms, e.g., binge eating [47]. Additionally, CR or the intent to restrict intake has been

associated with the onset of eating disorders, including anorexia [48] and bulimia nervosa [49], and binge eating disorder [50]. Hence, there is a need to examine both the benefit and potential harm of CR in humans, particularly for people who are not obese, and to answer important safety questions before CR is recommended [51,52].

In our study, at baseline months 3 and 6, participants completed an assessment battery that included: 1) the Multifactorial Assessment of Eating Disorder Symptoms (MAEDS), which measures six symptom domains associated with eating disorders (binge eating, purgative behavior, depression, fear of fatness, avoidance of forbidden foods, restrictive eating) [53], 2) the Eating Inventory, which measures dietary restraint, disinhibition, and perceived hunger [54], and 3) the Body Shape Questionnaire (BSQ) [55], which measures concern about body size and shape.

As reported by Williamson et al. [56], the three “dieting” groups in CALERIE, including the CR group, reported higher dietary restraint scores in comparison to the Control group at months three and six, but measures of eating disorder symptoms did not increase and some decreased. All groups, except the control group, reported a significant reduction in disinhibition at month six and binge eating, measured by the MAEDS, decreased for all four groups at months three and six. Concern about body size/shape, measured by the BSQ, decreased at three and six months among the three dieting groups but did not change in the control group. The Fear of Fatness and Purgative Behavior subscales of the MAEDS did not change during CR.

b. Subjective feelings of hunger

The ability of people to follow CR could be limited by feelings of increased hunger. We evaluated change in appetite ratings during CR using the perceived hunger scale of the Eating Inventory [54] and the Visual Analogue Scales (VAS), which have been found to be reliable and valid measures of appetite: hunger, fullness, desire to eat, satisfaction, and prospective food consumption [57]. During the six-month study, appetite ratings, measured with VAS, changed, but the change among the dieting groups were not significantly different than the control group. Moreover, based on the perceived hunger scale of the Eating Inventory, hunger was reduced in the CR group at month six [56].

c. Quality of Life and Mood

The Minnesota Semi Starvation study [43] indicated that CR can negatively affect mood, and therefore the effect of CR on mood and quality of life (QOL) becomes an important factor when considering the feasibility of CR in humans. During CALERIE Phase I, the Medical Outcomes Study Short-Form 36 Health Survey (SF-36) [58,59] was used to measure QOL, and the Beck Depression Inventory II [60] and depression scale of the MAEDS were used to measure mood. Our results indicate that depressed mood, measured by the BDI-II, did not change during the trial. Additionally, in the CR group, scores on the MAEDS depression subscale decreased at three and six months in comparison to baseline [56]. These results indicate that CR had no negative effect on mood during this trial and, in fact, symptoms of depressed mood, measured with the MAEDS, decreased in the CR group.

The SF-36 was used to test the effects of CR on two components of QOL - physical functioning and vitality. All dieting groups, but not the control group, had improved physical functioning during the trial. For the CR group, physical functioning was significantly improved from baseline to month three and baseline to month six. CR had no significant effect on vitality.

d. Cognitive Function and Performance

Self-reported dieting or calorie restriction has been associated with deficits in cognitive performance (e.g., memory and concentration deficits) [61,62]. Nevertheless, cognitive

impairment is frequently mediated by preoccupation with food and body weight [63], suggesting that obsessive thoughts about food and weight, rather than CR, negatively affect cognitive performance. If CR has negative effects on cognitive performance, the feasibility of CR in humans is in doubt.

During the CALERIE trial, cognitive performance was evaluated empirically at baseline and months three and six with a comprehensive neuropsychological battery [64]. Verbal memory was measured with the Rey Auditory and Verbal Learning Test (RAVLT) [65], short-term memory and retention with the Auditory Consonant Trigram (ACT) [66,67], visual perception and memory with the Benton Visual Retention Test (BVRT) [68], and attention/concentration with the Conners' Continuous Performance Test-II (CPT-II) [69]. During CR, no pattern of memory or attention/concentration deficits emerged and effect sizes were small, indicating that no more than 7% of the variance in change in cognitive performance was due to treatment arm. The degree of daily energy deficit also was not correlated with change in cognitive performance; hence, these data indicate that CR did not have a negative effect on cognitive performance [64]. All the effects of caloric restriction on psychological and behavioral outcomes are summarized in Table 1.

The psychological and behavioral findings from CALERIE provide important information about the feasibility and safety of CR in humans. Calorie restriction was not associated with the development of eating disorder symptoms, decreased quality of life, depressed mood, or cognitive impairment. In fact, many of these endpoints improved, and changes in subjective ratings of appetite were similar in the CR group to those of the control group. These results suggest that CR might be feasible and have few unintended consequences, at least among overweight individuals. Additional research is needed to determine the feasibility and safety of CR in other samples.

Conclusion

While the rodent and primate data indicate that lifespan extension is possible with CR, collective analysis of the rodent data suggest that intensity and onset of CR required to induce these effects is probably not suitable for many individuals [70]. Epidemiological studies certainly support the notion that a reduced energy intake that is nutritionally sound improves age-associated health. While results of the first randomized trials of CR, albeit short in duration suggest a reduction in risk of age-related disease and improvements in some biomarkers of longevity, the ultimate effect of this intervention on lifespan in humans will probably never been determined in the scientific setting. In our short-term study, calorie restriction was not associated with the development of eating disorder symptoms, decreased quality of life, depressed mood, or cognitive impairment all probably indicating the feasibility and safety of CR in humans. However, it is a challenge for most individuals to practice caloric restriction in an "obesogenic" environment so conducive to overfeeding. Only a very few will be able to practice a lifestyle of caloric restriction and probably benefit from it. There is therefore a need for the search for organic or inorganic compounds that mimic the biological effects of CR. If such compounds often called "CR mimetics" (such as resveratrol) prove viable in humans, individuals for the most part will opt to enjoy the effects of anti-aging via a 'pill' rather than CR.

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Figure 1. Can calorie restriction improve biological age and extend chronological age?

This figure summarizes some of the tentative biomarkers of aging. It is hypothesized that calorie restriction will change the biological trajectory of these biomarkers and therefore improve biological age and extend chronological age. For example, the left panel shows an individual aged 75 yr. With prolonged calorie restriction it is hypothesized that fasting insulin and oxidative damage will be reduced in this individual. Therefore an individual although 75 will have a biological age 17 years younger. Similarly the individual on the right at 90 years with prolonged calorie restriction will be biologically similar to an individual aged 66 years.

Figure 2. The effect of calorie restriction on core body temperature

Core body temperature, a possible biomarker of longevity, was significantly reduced after six months of calorie restriction [6]. Not only did calorie restriction decrease mean 24h temperature, minimal and maximal temperatures and the average through day and night times were also reduced. The top panel shows the mean change in 24h temperature as well as mean temperature change during the day and night and also the mean minimal and maximal temperature. The bottom panel shows a typical core temperature trace before and after six months of calorie restriction.

Table 1

Summary of the physiological and psychological/behavioral responses to six months of calorie restriction in humans. Results are for the Pennington CALERIE randomized clinical trial [6].

PHYSIOLOGICAL RESPONSES	PSYCHOLOGICAL/BEHAVIORAL RESPONSES
Body Composition ↓ Fat mass ↓ Fat-free mass ↓ Abdominal fat (visceral and subcutaneous) ↓ Abdominal fat cell size ↓ Intra-hepatic lipid content ↔ Intra-myocellular lipid content	Development of eating disorder symptoms ↓ Disinhibition ↓ Binge eating ↓ Concern about body size and shape ↔ Fear of fatness ↔ Purgative behavior
Diabetes Risk Factors ↓ Insulin sensitivity (not significant) ↓ Acute insulin response to glucose	Depressed mood ↓ MAEDS Depression scale ↔ Beck Depression Inventory II
Cardiovascular disease risk ↓ 10-year risk ↓ Blood pressure ↑ HDL-C ↓ Triacylglycerol (TG) ↓ Factor VIIc ↔ Fibrinogen, homocysteine, endothelial function	Subjective feelings of hunger ↓ Eating Inventory, Perceived Hunger Scale
Biomarkers of Longevity ↓ Fasting insulin ↓ Core body temperature ↔ DHEA-S	Quality of life ↑ Physical functioning ↔ Vitality
Energy Expenditure ↓ 24-h sedentary energy expenditure Metabolic adaptation for 24-h energy expenditure ↓ Sleeping metabolic rate (SMR) Metabolic adaptation for SMR	Cognitive Performance ↔ Verbal memory ↔ Short-term memory and retention ↔ Visual perception and memory ↔ Attention/concentration
Endocrinology ↓ T3 ↓ T4 ↔ GH ↔ IGF-1 ↓ Ghrelin	
Physical Activity ↓ Physical activity level (TDEE adjusted for SMR) ↔ Spontaneous physical activity	