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Caloric Restriction in Humans

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Abstract

Studies on mice and rats have demonstrated that calorie restriction (CR) slows primary aging, has a protective effect against secondary aging, and markedly decreases the incidence of malignancies. However, the only way to determine whether CR "works" in humans is to conduct studies on people. Such studies are difficult to perform in free-living people. While research on CR in humans is still at an early stage, a modest amount of information has accumulated. Because it is not feasible to conduct studies of the effects of CR on longevity in humans, surrogate measures have to be used. Preliminary information obtained using this approach provides evidence that CR provides a powerful protective effect against secondary aging in humans. This evidence consists of the finding that risk factors for atherosclerosis and diabetes are markedly reduced in humans on CR. Humans on CR also show some of the same adaptations that are thought to be involved in slowing primary aging in rats and mice. These include a very low level of inflammation as evidenced by low circulatory levels of c-reactive protein and TNFα, serum triiodothyronine levels at the low end of the normal range, and a more elastic "younger" left ventricle (LV), as evaluated by echo-doppler measures of LV stiffness.

INTRODUCTION

Since the initial report by McCay et al. (McCay *et al.*, 1935) that caloric restriction (CR) increases maximal longevity in rats, there have been hundreds of studies showing that CR slows aging in yeast, flies, worms, fish, mice and rats. The studies on mice and rats have demonstrated that CR (defined as calorie restriction without malnutrition) slows primary aging, has a protective effect against secondary aging, and markedly decreases the incidence of malignancies (Weindruch and Sohal, 1997). As used here, secondary aging is defined as the deterioration in tissue structure and biological function that is secondary to disease processes and harmful environmental factors. Protection against secondary aging results in rectangularization of the survival curve with an increase in average longevity but no increase in maximal longevity. Primary aging is the inevitable, progressive decline in tissue structure and biological function that occurs with advancing age, independently of disease or harmful lifestyle and environmental factors. Slowing of primary aging results in an increase in maximal longevity. While the demarcation between primary and secondary aging can become somewhat blurred, an understanding of the difference between these processes is essential for interpreting the results of studies of the effects of an intervention on longevity. CR is the only intervention

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that has consistently been shown to slow primary aging, as evidenced by an increase in maximal longevity, i.e. the finding that the oldest CR rats and mice survive ~20% to 50% longer than the oldest ad libitum fed controls (Weindruch and Walford, 1988).

The large expenditure of research funds, resources and time on studies of the effects of CR in yeast, worms, flies and rodents over the past 50+ years was, no doubt, largely motivated by the possibility that information obtained on these species has relevance to humans. However, while findings on rats, mice and perhaps also yeast, worms, and flies, can suggest possible mechanisms that are relevant to humans, the only way to determine whether CR "works" in humans is to conduct studies on people. Such studies are difficult to perform in free-living people and there is, therefore, little information available on the effects of CR, particularly long-term CR, in humans. This situation is starting to change and, while research on CR in humans is still at an early stage, a modest amount of information has accumulated.

Okinawan Centenarians

Severe, long-term CR has been a fact-of-life for many human populations throughout history, and is still prevalent among the poor in third world countries. However, these natural experiments have generally not provided information regarding the effect of CR on health and longevity, because low calorie diets necessitated by poverty are frequently deficient in essential nutrients and because of the high prevalence of acute and chronic infectious diseases in these populations. An exception to this pattern is the older generation of Okinawans who, because of poverty, were so severely calorie restricted that their growth was stunted (Chan *et al.*, 1997; Kagawa, 1978). However, public health measures and quality of the diet on Okinawa were sufficiently good to prevent the high prevalence of nutritional deficiencies and infectious diseases present among the poor in many third world countries. It is interesting, relative to the possible effects of CR on human longevity, that there are more centenarians per 100,000 people in Okinawa than in other parts of the world including the USA and Western Europe (Chan *et al.*, 1997). The Okinawan centenarians have, therefore, been cited as evidence that CR may slow aging in humans. However, although the percentage of very old people is higher in Okinawa than elsewhere, the oldest people in Okinawa are no older than the oldest people in other parts of the world who were not calorie restricted. This is in contrast to the finding in CR rats and mice that the oldest CR animals are older than the oldest ad libitum fed controls.

Studies on Rhesus Monkeys

It seems unlikely that it will ever be established with certainty whether CR increases maximal lifespan in humans. However, there are two studies of CR in Rhesus monkeys in progress, one at the University of Wisconsin at Madison, the other at the National Institute on Aging's, Gerontology Research Center, that should within the next 15–20 yr determine whether CR increases maximal longevity in non-human primates. These studies have already shown that CR protects against development of insulin resistance and diabetes, improves risk factors for atherosclerosis, decreases triodothyronine level, metabolic rate and body temperature, lowers decreases oxidative damage, decreases IGF-1 and IL-6 levels, and delays senescence of the immune system(Messaoudi *et al.*, 2006; Lane *et al.*, 1996; Lane *et al.*, 1999; Kemnitz *et al.*, 1994; Zainal *et al.*, 2000).

Studies in Humans

Because it is not feasible to conduct studies of the effect of CR on longevity in humans, surrogate measures have to be used. One approach is to determine whether humans undergo the same biological adaptations to CR that occur, and may be involved in slowing primary aging, in rodents. Another is to determine the effects of CR on risk factors for secondary aging. A third approach is to measure physiological variables that deteriorate progressively with aging, i.e. biomarkers of aging.

CR in Biosphere 2

Biosphere 2 is an enclosed ~3 acre space which was designed to be an "ecological mini-world". Eight volunteers were sealed inside Biosphere 2 for two years. During much of this period, food availability was severely limited because the amount of food they were able to grow was less than planned. The BMI of the 4 men decreased 19% to 19.3 ± 0.9 kg/m and the BMI of the 4 women decreased 13% to 18.5 ± 1.2 kg/m. Changes that occurred in response to this food shortage included marked reductions in blood pressure, fasting blood glucose, insulin, cholesterol, triodothyronine (T3) and white blood cells (Walford *et al*., 2002).

CALERIE Phase 1

CALERIE (Comprehensive Assessment of Long-Term Effects of Reducing Calorie Intake) is a research program that involves three research centers (Tufts University, Pennington Biomedical Research Center, and Washington University) and a coordinating center (Duke University) that was initiated by the National Institute on Aging (NIA), and is supported by NIH Cooperative Agreement AG204087 from the NIA, to obtain information on the effects of sustained CR in humans. The Phase 1 of CALERIE consisted of three pilot studies to determine whether an investigation of the effects of long-term CR in free-living humans is feasible and to obtain preliminary data on the adaptive responses to CR. The study at Tufts involved 12 mo of 25% CR in 24–42 yr old, healthy, overweight (BMI 25–29.9 kg/m) women and men. The study at Pennington involved 6 mo of 25% CR in healthy, overweight women and men aged 25 to 50 yr. The Washington University Phase 1 study involved 12 mo of 20% CR in 50 to 60 yr old, healthy, overweight women and men.

In the Pennington Phase 1 CALERIE study, the 6 mo of CR resulted in a 10% decrease in body weight, significant decreases in core body temperature, 24h energy expenditure and T3, body fat mass, fat-free mass, visceral adipose tissue, subcutaneous adipose tisse, fat cell size, intrahepatic fat, and fasting insulin, and an improvement in insulin sensitivity, (Heilbronn *et al.*, 2006; Larson-Meyer *et al.*, 2006; Redman *et al.*, 2007). In the Washington University Phase 1 CALERIE study, the 12 mo of CR resulted in a 10.7% decrease in body weight with a decrease in BMI from 27.2 ± 0.6 to 24.4 ± 0.6 kg/m^2. Total body fat mass, fat free mass, visceral fat mass, and subcutaneous abdominal fat mass, leptin, fasting insulin, and glucose and insulin areas under the oral glucose tolerance curve decreased significantly, while insulin sensitivity index increased in response to the CR (Racette *et al.*, 2006; Weiss *et al.*, 2006; Villareal *et al.*, 2006). Additional findings from these studies will be published in the near future.

Long-term severe CR results in very low body fat content. The participants in Phase 1 of CALERIE were initially overweight and had BMIs in the upper normal to moderately overweight ranges at the end of the study period. Thus, the information provided by these studies may be more relevant to the effects of weight loss than of chronic severe CR. However, Phase 1 did demonstrate that CR is feasible in free-living humans and has led to implementation of Phase 2 of CALERIE. In Phase 2 the participants are healthy men and women in the 25 to 45 yr age range, with BMI's in the 22 to 28 kg/m^2 range. A major effort is being made to recruit individuals with BMIs below 25 Kg/m^2 in the hope that a significant number of participants will achieve BMI's in the range that is attained by people practicing severe long-term CR (i.e. 18–20 kg/m^2). The intervention involves a 25% decrease in calorie intake for two years. The same three sites and coordinating center that conducted Phase 1 are involved in Phase 2 of CALERIE. The Phase 2 study should be completed in 2011.

Data obtained on members of the Caloric Restriction Society—The members of the Caloric Restriction Society (CRS) are restricting their food intake because they believe, based on the studies on laboratory animals, that CR will protect them against the disease processes responsible for secondary aging and slow the primary aging process. We have obtained data

on members of the CR Society who came to our laboratory to be examined. Most of the CRS members are men, and only 4 of those we have studied are women. In our initial study we measured risk factors for atherosclerosis in 18 CR Society members, average age 50 ± 10 yr, who had been practicing CR for an average of 6 yr, and 18 healthy age matched individuals eating typical American diets. The CR group had a BMI of 19.6 ± 1.9 kg/m^2 compared to a value of 25.9 ± 3.2 kg/m^2 for the comparison group. Total body fat averaged 6.7% in the CR men and 22.4% in the comparison group men. Total serum cholesterol, LDL cholesterol, total chol/LDL chol ratio were all markedly lower, while HDL cholesterol was higher in the CR than in the comparison group. The CRS members' average serum cholesterol, LDL cholesterol and triglyceride values all fall in the lowest 10% for people in their age groups (Fontana *et al.*, 2004). Fasting plasma insulin and glucose values were also significantly lower in the CR than in the comparison groups. One of the most remarkable findings in the CRS members is their extremely low blood pressure, with a systolic BP of ~100 mm Hg and a diastolic BP of ~60 mm Hg. A number of the CRS members have provided us with records of their serum lipid and blood pressure values, obtained through their personal physicians before they began CR and after ~1 year of CR. As shown in Table 1, their initial values were close to the 50th percentile for middleaged people in the U.S.

The CRS members appear to have low levels of chronic inflammation, as reflected in significantly lower circulating levels of C-reactive protein and TNFα than healthy, age-matched controls (Fontana *et al.*, 2004; Meyer *et al.*, 2006). The CRS members' serum triiodothyronine levels are lower than those of age-matched controls and fall in the low normal range (Fontana *et al.*, 2006). Left ventricular (LV) diastolic function has been evaluated in 25 CRS members, aged 53±12 yr, using transmitral flow, Doppler tissue imaging (Meyer *et al.*, 2006). Transmitral Doppler flow diastolic function indexes were similar to those of ~16 yr younger individuals, and measures reflecting LV stiffness were significantly lower than in controls, suggesting reduced LV fibrosis. All of the above effects of CR in humans have also been observed in rodents. Some of the data obtained by us on the CRS members up to January, 2007 is summarized in Table 2. The average values include previously published data and data obtained more recently on additional subjects.

In conclusion, although research on the effects of CR in humans is still at a very early stage, available information suggests that CR reduces the risk of developing Type 2 diabetes and atherosclerosis, and induces a number of the same adaptive responses that occur in CR laboratory animals.

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Table 1

Atherosclerosis risk factors in CR Society members before and after starting CR

	Before CR	**1.0±0.3 y) CR**	**6.5±4.8 y CR**
Body mass index (kg/m^2)	23.7 ± 2.6 (33)	20.3 ± 2.0 (28)	19.6 ± 1.6 (33)
Total cholesterol (mg/dl)	211 ± 36 (24)	165 ± 33 (16)	159 ± 36 (24)
LDL-cholesterol (mg/dl)	124 ± 37 (20)	94 ± 21 (14)	89 ± 30 (20)
HDL-cholesterol (mg/dl)	47 ± 8 (20)	59 ± 13 (14)	64 ± 21 (20)
Total chol.:HDL-chol. ratio	4.5 ± 1.1 (20)	2.9 ± 0.6 (14)	2.6 ± 0.5 (20)
Triglycerides (mg/dl)	134 ± 81 (24)	68 ± 22 (16)	49 ± 14 (24)
Systolic blood pressure (mmHg)	131 ± 15 (20)	112 ± 12 (14)	101 ± 9 (20)
Diastolic blood pressure (mmHg)	82 ± 9 (20)	71 ± 7 (14)	61 ± 7 (20)

Values are means ± SD. Number of subjects at each timepoint is given in parenthesis.

Table 2

Summary of data obtained on CR Society members

	Western Diet	Calorie Restricted
Age (y) (33)	52.3 ± 10	51.4 ± 12
Male:female	29:4	29:4
Body mass index (kg/m^2) (33)	24.8 ± 3.2	19.6 ± 1.6†
Total body fat (%) (33)	23.1 ± 7	8.4 ± 7†
Truncal fat (%) (33)	23.4 ± 9.7	4.6 ± 5.7†
Systolic blood pressure (mm Hg) (33)	130 ± 13	103 ± 12†
Diastolic blood pressure (mm Hg) (33)	81 ± 9	63 ± 7†
Total cholesterol (mg/dl) (33)	202 ± 33	162 ± 34†
LDL-cholesterol (mg/dl) (33)	122 ± 30	86 ± 24†
HDL-cholesterol (mg/dl) (33)	52 ± 15	64 ± 18*
Total cholesterol:HDL-cholesterol ratio	4.2 ± 1.2	2.5 ± 0.5†
Triglycerides (mg/dl) (33)	143 ± 93	58 ± 18†
Glucose (mg/dl) (33)	95 ± 9	84 ± 8†
Insulin (μU/ml) (33)	7.4 ± 6	1.5 ± 0.9†
TNFα (pg/ml) (28)	1.5 ± 0.9	0.7 ± 0.5*
C-reactive protein (mg/L) (31)	1.1 ± 1.2	0.2 ± 0.3†
TGFβ1 (ng/ml) (31)	22.1 ± 6.6	14.9 ± 3.1†
Triodothyronine (ng/dl) (28)	91 ± 13	74 ± 22†

Values are means ± SD for the number of subjects given in parenthesis.

*P<0.01

†P<0.001 CR versus Western Diet.