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OPINION

Caloric restriction and human longevity: what can we learn from the Okinawans?

D. Craig Willcox · Bradley J. Willcox · Hidemi Todoriki · J. David Curb · Makoto Suzuki

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Abstract Caloric (or dietary) restriction (CR) extends lifespan and lowers risk for age associated diseases in a phylogenetically diverse group of species. Whether prolonged CR increases average or maximum lifespan or promotes a more youthful physiology in humans at advanced ages is not yet known. However, available epidemiological evidence indicates that CR *may already have* contributed to an extension of average and maximum life span in one human population and appears to have lowered risk for age associated chronic diseases in other human populations. We review the human studies in the context of a special human population, older Okinawans, who appear to have undergone a mild form of prolonged CR for about half their adult lives.

Keywords Caloric restriction · Okinawa · Maximum life span · Healthy aging · Diet · Longevity

D. C. Willcox (✉)
College of Nursing, Okinawa Prefectural University, 1-24-1 Yogi, Naha, Okinawa 902-0076, Japan
e-mail: willcox@okinawa-nurs.ac.jp

B. J. Willcox · J. D. Curb · D. C. Willcox
Pacific Health Research Institute, 846 South Hotel Street, Suite 301, Honolulu, HI 96813, USA

B. J. Willcox · J. D. Curb
Departments of Geriatric Medicine and Medicine, John A. Burns School of Medicine, University of Hawaii, 1356 Lusitana Street, 7F, Honolulu, HI 96813, USA

H. Todoriki
Faculty of Medicine, University of the Ryukyus, Department of Environmental and Preventive Medicine, 207 Vehara, Nishihara, Okinawa 903-0215, Japan

M. Suzuki
Professor Emeritis, University of the Ryukyus, 207 Uehara, 903-0215, Nishihara-Cho, Okinawa, Japan

Introduction

Caloric (or dietary) restriction (CR) is the only consistently reproducible experimental means of extending mean and maximum lifespan and markedly decreasing morbidity in a phylogenetically diverse group of short lived laboratory mammals. Studies underway with longer-lived species such as non-human primates are also showing promising early results regarding the life-extending physiological effects seen in rodents and other animals (Roth et al. 2001; Mattison et al. 2003; Lane et al. 2004). The question of whether or not CR would work in humans may be one of the most significant unanswered questions in biogerontology.

We take the position that CR not only *will* work but in fact available epidemiological evidence indicates that CR *may already have* contributed to an extension of average and maximum life span in one human population and appears to have lowered risk

for age associated chronic diseases in other human populations. We review the human studies in the context of a special human population that we believe has undergone prolonged CR while also maintaining a high quality diet—a necessary condition for CR to manifest its beneficial effects.

CR studies and effects in humans

Short-term studies of humans under various CR paradigms have shown dramatic changes in biology similar to prior studies in other animals. While some effects appear partly mediated by reduction of fat mass, multiple mechanisms have been proposed including altered insulin signaling, reduced free radical damage, and hormesis, among others. This evidence has been reviewed elsewhere and we will concentrate on long term human studies (Heilbronn and Ravussin 2003; Masoro 2005; Dirks and Leeuwenburgh 2006).

Recent data from individuals (18 subjects) undertaking a voluntary long-term CR regimen supports what would be expected by the short term studies. Long term caloric restriction for periods of 3–15 years (average of 6 years) has shown it to be highly effective in reducing the risk for atherosclerotic arterial disease, the leading cause of morbidity and mortality in Western societies, by changing key biochemical, hormonal and metabolic parameters (Fontana et al. 2004). CR also appears to ameliorate the decline in diastolic heart function that occurs with human aging (Meyer et al. 2006). A key question is whether or not these systemic changes are reflective of a more youthful physiology and will enhance health and lifespan if continued over a longer time period.

A recently published 25 years follow-up report from the Baltimore Longitudinal Study of Aging (BLSA) suggests that this might indeed be the case. The BLSA noted that healthy men who displayed three ''biomarkers of the CR phenotype''—lower insulin levels, lower body temperature and a slower decline in levels of the hormone dehydroepiandrosterone sulfate (DHEA-S) also had significantly longer survival (Roth et al. 2002). Furthermore, similar findings have also been seen in the Honolulu Heart Program cohort where blood glucose in middle age strongly predicts late life survival (Rodriguez et al. 1999). More human studies are needed to confirm these preliminary findings and are currently underway, such as the CALERIE trials, but they do not address longevity as an outcome (Heilbronn and Ravussin 2003).

Only one long-term epidemiological prospective study (>30 years) has directly addressed the issue of caloric intake and human longevity. This 36-year follow-up study reported a weak trend for lower all-cause mortality in healthy non-smoking Japanese-American men suggesting that those who consumed a modestly low energy intake (85% of group mean) had the lowest risk for all-cause mortality (Willcox et al. 2004). There was higher mortality risk when caloric intake dropped below 50% of the group mean. This is consistent with previous animal findings that show decreased risk for mortality from age associated diseases and increased life span under a CR regimen of up to 50% restriction.

The Okinawa findings

Older Okinawans exhibit the CR phenotype

Low caloric intake was first reported in the Okinawan population by Hokama et al. (1967) who showed that Okinawan school children consumed only 62% of the calories of other Japanese school children. Kagawa (1978) confirmed low caloric intake (83% of Japan average) in the Okinawa adult population from the 1972 Japan National Nutrition Survey and documented anthropometric and morbidity data from older Okinawans that were consistent with CR. Kagawa (1978) hypothesized that this may have been partly responsible for the long and healthy lives of Okinawans. Death rates from heart disease, cancer and cerebral vascular disease were found to be only 60 to 70% of that of the Japan average and the all-cause mortality rate for 60–64 year olds was only half that of other Japanese. A later study published by Chan et al. (1997) also reported dietary and phenotypic data in Okinawan septuagenarians and centenarians consistent with CR.

Our recent analysis of long-term trends in whole population caloric intake and energy balance for the years beginning in 1949 demonstrates that the Okinawan septuagenarian population appeared to be in a relative ''energy deficit'' consistent with CR until the late 1960s, eating approximately 11% fewer

calories (approximately 1,785 kcal per day) than would normally be recommended for maintenance of body weight according to the Harris-Benedict equation (Willcox et al. Unpublished data). The body mass index (BMI) of adult Okinawans also remained stable at a very lean 21 kg/m^2 and peak body weight was reached in young adulthood and appeared relatively stable until elderly ages (Willcox et al. Unpublished data). These dietary and anthropometric data are consistent with adaptation to a long-term energy deficit and fit proposed epidemiologic definitions by a recent US National Institutes of Health panel (see Lee et al. 2001) of the human CR phenotype (i.e. no weight gain after early adulthood).

Moreover, nutritional studies suggest that the traditional Okinawan diet, with its high intake of green leafy and yellow root vegetables, sweet potatoes as a dietary staple, and soy as a principle protein supplemented by small amounts of fish and meat, was adequate in most nutrients and particularly high in antioxidant vitamins (Sho 2001; Suzuki et al. 2001; Todoriki et al. 2004; Willcox 2005).

Was there a CR effect?

If a CR phenomenon occurred for the current generation of elderly Okinawans then there should be biomarker evidence of CR-linked delayed physiological aging. Thus, it is of keen interest that recent findings from our ongoing study of Okinawa's elderly population show that Okinawan septuagenarians, who would have undergone CR until at least middle age according to the previous population data, exhibit higher DHEA levels when compared to age-matched Americans not subjected to CR (Willcox et al. Unpublished data). In addition, if delayed aging occurred in Okinawans, then there should be a rightward shift in the survival curve, with increases in both average lifespan and maximum lifespan. Indeed, survival curves for Okinawan, Japanese and U.S. populations calculated based on life table data for the year 1995 do show increases in both average and maximum lifespan in the Okinawan population compared to Japanese and American populations, consistent with CR. Average lifespan (measured as 50th percentile survival) and maximum lifespan (measured as 99th percentile survival) in the Okinawan, Japanese and U.S. populations were 83.8 and 104.9 years, 82.3 and 101.1 years, and 78.9 and 101.3 years, respectively (Willcox et al. Unpublished data).

Finally, age-adjusted mortality for specific age-related diseases (especially cardiovascular diseases) is extremely low in elderly Okinawans compared to other age-matched Japanese or Americans (Kagawa 1978; Suzuki et al. 2001).Thus, life expectancy at *older ages* is extremely long in Okinawa. For the septuagenarian cohort, life expectancy from age 65 is the longest in Japan, and possibly the world, at 24.1 years for females and 18.5 years for males (Japan Ministry of Health, Labor and Welfare, 2005). This compares to 22.5 years and 17.6 years for the same birth cohort in mainland Japan (Japan Ministry of Health, Labor and Welfare 2000) and 19.3 years and 16.2 years for corresponding U.S. birth cohorts of females and males respectively (U.S. Centers for Disease Control and Prevention 2003). Also consistent with a longer life expectancy at older ages is the high numbers of centenarians at approximately 50 per 100,000 or about 4–5 times the average for most industrialized countries (Japan Ministry of Health, Labor and Welfare 2005).

Other factors may also be contributing to the exceptional longevity of the Okinawans such as genetic factors, specific nutritional components of the diet (high anti-oxidants), social support and/or health care (Takata et al. 1987; Goto et al. 2003; Todoriki et al. 2004; Suzuki et al. 2001, 2004; Willcox 2005; Willcox et al. 2006). However, the forces of morbidity and mortality act most strongly at older ages and it is at these ages one would expect to see the most marked phenotypic differences and the most marked survival advantage, had CR occurred in the Okinawans, and indeed this is the case.

Should we restrict our calories?

Some scientists who study the mechanisms of aging suggest that it is unlikely that the maximum lifespan of humans can be extended by any intervention, including caloric restriction (Hayflick 2004). It has also been argued that while CR is likely to be almost universal in its beneficial effects on longevity, the benefit to humans is likely to be small, even if humans restrict their caloric intake substantially and over long periods of time (Phelan and Rose 2005). The latter argument derives from observations of

complex differences between species (such as amount of energy allocated to reproduction) and the fact that underlying physiological mechanisms that determine longevity are not necessarily the same between species. Furthermore, there are potential health concerns, particularly if practiced incorrectly (too severe) or at vulnerable (too young, too old, pregnancy) life stages (Le Bourg 2005; Dirks and Leeuwenburgh 2006).

While fully acknowledging that the nature of the life-extending action of CR may differ among species, we believe these views to be overly pessimistic and not reflective of the available evidence. However, we believe that people should not attempt to restrict calories to the extreme levels seen in animal studies (up to 60%) because human studies, although promising, have not fully addressed issues such as quality of life and other potential side effects. With that caveat in mind, cautious approaches to lowering calories (mild CR) among adults while maintaining optimal nutrient intakes would still likely result in significant health benefits. In fact, recent findings show that even 8% CR has beneficial effects on specific biochemical and inflammatory biomarkers (Dirks and Leeuwenburgh 2006).

We cite the following reasons for a more optimistic view of the potential benefits of the CR lifestyle for human beings: First, the accumulated evidence of 70 years of CR studies suggests that CR is an extremely ancient and very important survival mechanism which appeared early in the evolution of eukaryotes. Therefore it appears to be strongly conserved throughout the phylogenetic scale (from yeast to mammals). As such, it would be unusual if it did not work in some positive capacity in humans as well. Second, studies in progress with non-human primates (who share over 95% of our genes and have similar reproductive physiology) on a CR regimen, while not yet conclusive, are showing early results consistent with previous animal data. Third, short-term and longer-term studies of humans under a true CR paradigm have shown dramatic changes in physiology and metabolic shifts similar to other animals. Fourth, our research shows that older Okinawans (ages-65 plus) exhibit a CR-like phenotype and ate a low calorie diet over a prolonged period of time. Calories in the Okinawan population were approximately 11% fewer than what would usually be recommended for their body weight and activity levels (based on the Harris-Benedict equation) but only for half their adult lives.

Yet, even with this mild CR-like regimen older Okinawans have gained an additional 6% survival time from age 65 (1.3 years) versus other Japanese and an additional 20% survival time (3.6 years) versus Americans. Given the large number of factors that influence human lifespan, this is also surprisingly similar to the gain in lifespan observed in prior animal studies (i.e. 10–20% calorie reduction leads to a 10–20% increase in lifespan). Most importantly, the Okinawans appear to have gained an increased health span, with almost a decade of disability-free life expectancy beyond what typical Western populations experience.

Lastly, while Okinawans were not consciously practicing CR, they did develop cultural habits that led to the kind of prudent food choices that maximize nutritional properties of foods while minimizing caloric density as would be the favored strategy for anyone who attempts a CR regimen. Simply avoiding calorie-dense refined sugars, saturated fats and processed foods and replacing them with nutrient-dense but calorie poor vegetables, fruits and legumes will not only likely lead to spontaneous weight loss through lower caloric intake but would also result in a vastly increased intake of health-enhancing phytonutrients, including key vitamins and minerals, antioxidants and flavonoids. Practicing a little restraint at the dinner table may also have its benefits. ''Eat until you are 80% full'' (or *hara hachi-bu*) is the advice that Okinawan grandmothers have given for years and the science of CR appears to be proving that the wisdom of the elders still rings as true as ever.

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