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Caloric Restriction, CR Mimetics, and Healthy Aging in Okinawa: Controversies and Clinical Implications

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Abstract

Purpose of Review—To examine the role of two nutritional factors implicated in the healthy aging of the Okinawans: caloric restriction (CR); and traditional foods with potential CR-mimetic properties.

Recent Findings—CR is a research priority for the U.S. National Institute on Aging. However, little is known regarding health effects in humans. Some CR-related outcomes, such as cause-specific mortality and lifespan, are not practical for human clinical trials. Therefore, epidemiological data on older Okinawans, who experienced a CR-like diet for close to half their lives, are of special interest. The nutritional data support mild CR (10–15%) and high consumption of foods that may mimic the biological effects of CR, including sweet potatoes, marine-based carotenoid-rich foods, and turmeric. Phenotypic evidence is consistent with CR (including short stature, low body weight, lean BMI), less age-related chronic disease (including cardiovascular diseases, cancer, and dementia) and longer lifespan (mean and maximum).

Summary—Both CR and traditional Okinawan functional foods with CR-mimetic properties likely had roles in the extended healthspan and lifespan of the Okinawans. More research is needed on health consequences of CR and foods with CR-mimetic properties to identify possible nutritional interventions for healthy aging.

Keywords

Caloric restriction; CR-mimetic; human; lifespan; healthspan

Introduction

Nutrition is among the most important means for mitigating age-associated chronic diseases. By some estimates, eighty percent of coronary heart disease (CHD) and type-2 diabetes

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mellitus (T2DM) and forty percent of cancers, may be prevented by modifying dietary habits, engaging in regular physical activity, and avoiding tobacco use [1,2,3]. Highlighting the importance of nutrition, a recent, large collaborative 20-year study found that dietary factors accounted for twenty-six percent of the risk for early death (the majority) and the most disability-adjusted life years lost in the US [4••].

The Okinawans are of special interest to this topic since they, by most measures, have the world's longest-lived population and nutritional factors appear to have played a key role [5,6,7]. The chronic disease profile of the older Okinawan population is especially impressive, with 80% less CHD mortality and 40% less cancer mortality than the U.S. population [5], and mirrors the estimates thought preventable by the W.H.O. and the C.D.C [1–3].

Some attribute the healthy aging phenomenon in Okinawa principally to nutritional factors, and caloric restriction (CR) is thought to be one key factor [5,6,8,9] . CR (also known as dietary restriction) is a well known research intervention for those who investigate the biology of aging in model organisms, and is a priority research focus for the U.S. National Institute on Aging—yet few data exist in humans [10•]. The most extensive analysis of the CR phenomenon in Okinawa was based on five decades of nutritional, phenotypic, epidemiologic and demographic data [5]. This analysis utilized dietary surveys and population health data from the 1950s to the 1990s to demonstrate that the adult population appeared to be in a relative ''energy deficit'' consistent with CR until the late 1960s, eating approximately 11% fewer calories (1,785 kcal per day) than would normally be recommended for maintenance of body weight, according to the Harris-Benedict equation. Metabolic adaptations to such conditions included low body weight, shorter height, and low body mass index (BMI). Adult BMI was a lean 21 kg/m2, peak body weight was reached in young adulthood, and was relatively stable until elderly ages. These dietary and phenotypic data are consistent with adaptation to a long-term energy deficit and fit proposed epidemiologic definitions of CR by a U.S. NIH expert panel [11].

Consistent with a CR effect, prevalence and age-adjusted mortality for particular age related diseases (especially cardiovascular diseases, cancer and dementia) is low in elderly Okinawans compared to other Japanese or Americans [5,9] and life expectancy at older ages is long. Life expectancy from age 65 may be the longest in the world, at 24.1 years for females and 18.5 years for males. This compares favorably to 22.5 years and 17.6 years for the same birth cohort in mainland Japan and 19.3 years and 16.2 years for corresponding U.S. birth cohorts of females and males, respectively [9]. A rightward shift in the survival curve consistent with extended mean and maximum lifespan also strongly supports a CR effect [5]. CR is the only non-genetic intervention that has consistently shown an extension of maximum lifespan in model organisms of aging and the Okinawans are the only known human population to show an extension of maximum lifespan [5]. Consistent with this is a high prevalence of centenarians, with approximately 50 centenarians per 100,000 persons (~ 4–5 times the average for most industrialized countries) [9,12].

Despite these data there is still much controversy about the potential merits of human CR. The traditional low calorie Okinawan diet, and its association with the world's longest-lived people, is a particular magnet for such controversy [8,13,14•,15]. Therefore, this paper will present recent evidence on two important nutritional factors implicated with healthy aging in Okinawa: caloric restriction (CR) and traditional Okinawan foods that may mimic the biological effects of CR.

Caloric Restriction, Nutrient-Sensing Pathways and Healthy Aging

Perhaps the most controversial nutritional factor that may be implicated in Okinawan longevity is caloric restriction. CR (when not accompanied by nutritional deficiencies), is the most consistently reproducible experimental means of delaying morbidity and extending average and maximum lifespan in model organisms of aging (e.g. yeast, worms, flies, mice) but the effects in humans are unclear [10•,16•,17•,18••]. The anti-aging effect appears robust until restriction reaches about half the typical calorie intake of the model organism under study and was also observed in one human epidemiologic study [19]. It was previously thought that the anti-aging effect of CR could only be achieved through restriction of calories but recent work has demonstrated that restriction of other nutrients (i.e. particular amino acids) may also extend lifespan and healthspan, thus the use of the term “dietary restriction” is increasingly utilized [18••,20].

The biological basis of the CR phenomenon is not yet known, but may be linked to nutrient-sensing biological pathways, which modulate growth and biological systems responsible for stress resistance and, ultimately, aging [18••]. A growing consensus favors the hypothesis that this low nutrient intake induces “hormesis”, a low-level stress, which triggers the upregulation of stress resistance biological pathways, which include genes encoding for FOXO3 and MTOR [18••]. Both genes code for transcription factors that influence longevity of model organisms of aging. Interestingly, FOXO3 is one of only two genes that have been consistently shown to influence longevity in diverse human populations (the other gene is APOE) and it is strongly upregulated by CR. FOXO3 acts as a key checkpoint gene in the insulin-IGF-1 signaling pathway and helps regulate metabolism, oxidative stress, cell cycle, apoptosis and other mechanisms responsible for cell and organismal survival [21]. Therefore, there are biologically plausible explanations for why CR might enhance healthy human aging.

Human CR research has become an area of growing interest to the gerontological research community. The question of whether or not CR can delay incident age-associated diseases and extend lifespan in humans is a major, unanswered question in aging research [10•,18••]. Studies underway with nonhuman primates, although of mixed outcome, have demonstrated some results consistent with the model organism data [10• ,17•]. Human studies, by their nature, have been limited and mainly short term. Short-term studies of humans under various CR paradigms have shown dramatic changes in physiology similar to prior studies in model organisms [10•,22]. Longer term studies of humans who practice CR (from 3–15 years) have also shown adaptations consistent with the model organism data--including evidence for slower aging (e.g. delayed diastolic dysfunction of the heart) [22].

The Okinawans have long held the attention of CR researchers since they are perhaps the best human example of a naturally calorically restricted population (with adequate or even optimal nutrition) and the study of their healthspan, mortality patterns and lifespan may yield important clues as to long-term effects of human CR. Some argue that they might be naturally long-lived for genetic, or other reasons, but the rapid disappearance of the CR phenotype and longevity advantage in younger Okinawans(who did not experience CR) suggests otherwise. Willcox et al [7] show that Okinawans, who since the 1960s did not appear to be experiencing population-wide CR, now have a higher BMI across all age strata, higher prevalence of Type 2 diabetes, and worse cardiovascular risk factors than other Japanese. The Okinawan life expectancy advantage, which used to be the highest in Japan for all ages, is now restricted to older ages, consistent with a residual CR-related cohort effect in older Okinawans [7].

While these data support CR as a nutritional factor that influenced healthy aging and longevity in Okinawa there is still ongoing debate in the scientific community with regard to both the CR phenomenon and its purported health effects in Okinawans and other humans [8,13,15]. One argument that has been advanced is that the loss of health advantages in younger Okinawans is an epigenetic response to CR in prior generations [13]. However, the positive shift in energy balance due to higher caloric intake combined with a less active lifestyle (which has led to the highest obesity rates in Japan)and other lifestyle risk behaviors, provides ample explanation for the elevated risk factor profile and the loss of the life expectancy advantage in younger Okinawans (versus their mainland Japanese counterparts) [7,8,15].

Caloric Restriction Mimetics and Functional Foods in Okinawa

While there are several nutritional factors that are implicated in Okinawan longevity, in addition to CR, another nutritional factor that is receiving increasing attention is the health properties of particular foods from the traditional Okinawan diet [23]. Several of these foods may mimic the biological effects of CR, acting as caloric restriction “mimetics”.

CR mimetics, or compounds that provide the physiological benefit of CR without the need for restriction of calories, are under active investigation by many research groups [24,25]. The upside of CR mimetics could be large. If pharmaceutical, nutraceutical, and/or hormonal compounds can be developed that activate the same metabolic- and stress-response pathways induced by CR—without restriction of food intake—there could be an enormous potential impact for public health [24,25]. Several CR mimetics have received attention from government, pharmaceutical, and private foundation research organizations. The most widely studied compounds include rapamycin, resveratrol, and metformin [24–26]. Other functional foods that may act as CR mimetics, several of which are common in the traditional Okinawan diet, include sweet potato-based compounds, marine-based carotenoid-rich foods, turmeric, and various flavonoids, especially from soy foods [23].

The traditional Okinawan diet is a rich source for potential CR mimetics. In the Okinawan language, the term *nuchi gusui*, a term in common use, literally means “food is medicine” since commonly consumed dietary items, including foods, herbs and spices are also used as folk medicines [23]. Popular items that play dual roles as foods and traditional medicines are sweet potatoes (pulp, skin and leaves), bitter melon, turmeric, ginger, mugwort (Artemisia vulgaris), peppers (Piper hancei), and carotenoid-rich marine foods, among others. It is curious that in Okinawa so many food items might be thought to have medicinal properties but there may be a scientific basis for this—climate [27]. Compounds that have potential CR mimetic properties, such as carotenoids, flavonoids and other phytochemicals, are synthesized (mostly by plants) to help scavenge free radicals formed due to stress from extremes of heat, cold, or UV light. Since the sun in Okinawa is particularly strong many locally grown plants contain high quantities of these phytochemicals [28]. Bacterial and viral pathogens, insects, physical injury, and/or other stressors also trigger production of such compounds. Murakami et al. [28] investigated typical food items from Okinawa and compared them to typical food items from mainland Japan. Foods from Okinawa had, on average, stronger free radical scavenging properties. Of 138 food items they tested for anti-inflammatory action, many phytochemicals were promising anti-inflammatory agents, especially wild Okinawan turmeric (Curcuma longa L.) and Okinawan zedoary (Curcuma Zedoaria, white turmeric) both from the genus Curcuma, and the ginger (Zingiberaceae) family.

The most common compounds (such as polyphenols, flavonoids, terpenoids, sesquiterpenoids and others with strong anti-oxidant properties) initiate a cellular stress response and induce bimolecular adaptations collectively referred to as “hormesis” [23]. As previously noted, hormesis is a major hypothetical mechanism for the lifespan and healthspan enhancing effects of caloric restriction [25]. Davinelli, Willcox and Scapagnini [23] proposed that phytohormetic stress resistance involves the activation of Nrf2 signaling, a central regulator of the adaptive response to oxidative stress, and that this may form, in part, the basis for CR’s anti-aging effects. Oxidative stress is believed to be a principal mechanism of aging so the enhancement of anti-oxidative protection and the inhibition of free radical production are biological pathways that may protect against oxidative damage, mitigating risk for age associated disease and, perhaps, modulating the rate of aging.

Hormetic phytochemicals have received great attention for their potential pro-longevity effects and ability to act as sirtuin activators, the most notable being resveratrol [24,25]. Interestingly, several of these compounds are potent activators of FOXO3 transcription, a key transcription factor from the insulin-IGF-1 signaling pathway [29]. FOXO3 appears essential for caloric restriction to exert its beneficial effects [23]. Allelic variation in the FOXO3 gene is strongly associated with human longevity and this finding has been replicated in over 10 independent populations and is one of only two consistently replicated genes associated with human longevity [21]. This has generated great interest and multiple research groups are attempting to identify FOXO3’s functional component(s) [21]. Some promising functional foods and food compounds from the traditional Okinawan diet are reviewed below. Interestingly, several have been shown to modulate FOXO3 expression and modulate the insulin-IGF-1 signaling pathway, supporting a nutritional genomic effect of food and genotype.

Sweet Potato (Ipomoea batatas)

Since the 1600s, the sweet potato has formed the bulk of the Okinawan diet, accounting for well over half of caloric intake. The sweet potato is a dicotyledonous plant from the

Convolvulaceae family. The edible tuberous root is long and tapered, appears most commonly in yellow, purple, violet, red, and orange colors. The leaves and shoots (called *kandaba)* are eaten as greens in miso soup. Sweet potatoes consumed in Okinawa have several interesting nutritional characteristics that may have anti-aging effects.

One such characteristic is the protein called "sporamin". Sporamin is the major storage protein, composing over 80% of the total protein in the edible tuberous root, and exhibits biological functions that also include environmental defense and free radical inhibitory and scavenging activity [30]. Sporamin is expressed systemically in response to stress, such as wounding, environmental extremes, injury, pest and toxin defense.

In a recent study, phytonutrient concentrations and gene expression profiles were investigated in yellow, white, and purple sweet potatoes [31]. Purple sweet potatoes were found to have the highest total phenolic content. The major phenolic was 5-chlorogenic acid (5CGA). Others included quercetin 3-O rutinoside, kaempferol 3-O-rutinoside, petunidin 3-O-(p-coumaroyl) rutinoside-3-glucoside. The most common carotenoids were violaxanthin and lutein. Expression of most phenylpropanoid and carotenoid structural genes decreased during development and resulted in lower phytonutrient content in mature vs. immature sweet potatoes ("baby potatoes"). Other common phytonutrients, which vary by type of sweet potato, include phenolic acids, flavonols, anthocyanins, and carotenoids [31].

Marine-based Carotenoid-rich Foods

Marine-based carotenoid sources, such as seaweed, algae, and kelp are very low in caloric density, protein-rich, nutrient dense with ample carotenoids, folate, magnesium, iron, calcium, iodine, and several have been shown to act as CR mimetics [32–34]. The compounds characteristic of some marine foods, such as seaweed, include bioactive phytochemicals not present in land-based plants, such as the xanthophyll fucoxanthin, the polysaccharide fucoidan, astaxanthin and phlorotannins [32].

Fucoxanthin is a carotenoid pigment derived from chloroplasts of brown algae and most other brown-green kelp/plankton, which are common in the Okinawan diet and found in Undaria pinnatifida (Wakame), Hijikia fusiformis (Hijiki), Laminaria japonica (Kombu) and Sargassum fulvellum, among other marine foods. Recent work shows that fucoxanthin increases expression of uncoupling protein-1 (UCP-1) in white adipose tissue (WAT) mitochondria in the abdomen, increasing WAT oxidation of fatty acids and heat production [35]. Other studies have found antioxidant, anti-carcinogenic, anti-diabetic and anti-photo aging properties [35]. Studies of animal models show multiple beneficial effects on metabolism, including reduction of blood glucose and insulin and attenuation of weight gain, thereby holding promise as a potential dietary intervention for metabolic syndrome and related disorders [33,34,35].

Fucoidan is another marine-based carotenoid with interesting health properties. It is a sulfated polysaccharide found in popular Okinawan marine plant foods, mainly the seaweeds kombu, wakame, mozuku, and hijiki [36]. Research literature on fucoidans tripled between 2000 and 2010 and continues to grow. Fucoidan has several anti-carcinogenic properties that range from direct cytotoxic effects on cancer cells to inhibition of carcinogenesis through modulation of apoptosis, angiogenesis, local invasion, and metastasis [37]. Fucoidan also appears important in insulin signaling, a major biological pathway in aging. For example, a recent study of fucoidan extracted from Saccharina japonica was administered to normal and diabetic rodents and its effects on glycemia, insulin and serum lipid levels were evaluated [38]. The study demonstrated fucoidan had considerable hypoglycemic effects, possibly by stimulating pancreatic release of insulin and/or by reducing insulin metabolism. Lipid profile also improved in the rodents treated with fucoidan. In another study of rodents, mice that were fed a high fat diet for five weeks with or without fucoidan showed significant physiological differences [39]. The fucoidan supplemented group had significantly decreased weight gain and less liver and epididymal fat mass compared with the non-supplemented group. The mice supplemented with fucoidan also showed significantly reduced triglyceride, total cholesterol and low-density lipoprotein levels in the plasma. Liver steatosis induced by the high fat diet improved in the fucoidan-supplemented group. Furthermore, fucoidan affected expression patterns of adipose tissue genes, including peroxisome proliferator-activated receptor γ, adipose-specific fatty acid binding protein, and acetyl CoA carboxylase.

A third marine carotenoid common in the Okinawan diet is astaxanthin, a xanthophyll carotenoid. It has powerful, broad-ranging antioxidative properties and originates mainly from micro-algae but also is found in fungi and complex plants. Higher order marine life that feed on plant sources accumulate astaxanthin, such as crustaceans and reddish colored fish such as salmon [40]. As such, is makes its way into the Okinawa diet through widespread means Evidence suggests that that astaxanthin has promise for modulating aging through activation of the insulin signaling pathway and upregulation of the FOXO3 gene [41]. A recent review highlights promising astaxanthin-related clinical trials in model organisms and humans for agingrelated outcomes [42•].

Turmeric (Curcuma longa)

Originally from India, turmeric is from the rhizome of *Curcuma longa*, and belongs to the ginger family. Tumeric was likely brought to the Ryukyu Kingdom (now Okinawa prefecture) through the spice trade, in which the Ryukyu Kingdom was an avid participant. Curcumin, one of the major active compounds, is a phenolic compound concentrated in the roots of *Curcuma longa* and has been extensively studied for its numerous biological activities including antiinflammatory, antioxidant and anticancer properties [43]. The anti-inflammatory capacity of curcumin correlates with a reduction of the activity of nuclear transcription factors in the NFkβ signaling pathway, which regulate the transcription of several proinflammatory genes.

In the roundworm *C. elegans,* curcumin extended lifespan and reduced intracellular ROS and lipofuscin during aging. It also affected body size and the pharyngeal pumping rate (a measure of healthspan) but not reproduction of wild-type *C. elegans*. The lifespan extension in *C. elegans* was attributed to its antioxidative properties. Specific genes implicated were *osr-1, sek-1, mek-1, skn-1, unc-43, sir-2.1*, and *age-1* 44].

Tetrahydrocurcumin (THC), an active metabolite of curcumin has been shown to extend lifespan of Drosophila under normal conditions, by attenuating oxidative stress via FOXO and Sir2 modulation [45]. Curcuminoids may also affect mammalian longevity, as shown in mice fed diets containing THC starting at the age of 13 months, which showed significantly increased mean lifespan [46].

Epidemiological studies and clinical trials suggest that curcumin inhibits pathological processes that are involved with dementia, particularly Alzheimer's disease [47]. Interestingly, the prevalence of dementia among elderly population appears to be lower in the curcumin-consuming Okinawans when compared to the US or Japan populations [48]. Further studies on this issue are warranted.

Clinical Implications

Should we restrict our calories? Should we consume CR mimetics? First, the cumulative evidence of over seventy years of CR research demonstrates that CR is an ancient and important survival mechanism which appeared early in the evolution of eukaryotes. It is conserved across the phylogenetic scale, from yeast to mammals. Second, studies in progress with non-human primates on a CR regimen, show some support for the model organism data [10• ,17•]. Third, short-term and longer-term studies of humans under a true CR paradigm have shown dramatic changes in physiology and metabolic shifts consistent with model organisms [10•]. Fourth, Willcox et al. [23] demonstrated that older Okinawans ate a CR-like diet and exhibit a CR-like phenotype. Even with their mild CR-like diet, they only consumed this diet for up to half their lives, since they transitioned to positive energy balance and higher BMIs from the 1960s to present [7]. Yet 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[9]. This is comparable to lifespan increases observed in prior model organism studies. Perhaps most notable is that Okinawans gained *almost a decade* of additional disability-free life expectancy compared with Americans.

Conclusions

The traditional diet of the Okinawans, who by many measures are the world's longest-lived (and healthiest) people, provides many clues for research on the nutritional aspects of healthy aging and longevity. Two topics that are receiving increasing attention are caloric restriction and functional foods with CR-mimetic properties. We need to learn much more about CR and CR mimetics, before health recommendations can be made to the public. In particular, there may be ages where such interventions might be ineffective or result in adverse outcomes, such as before adulthood or in the elderly years. Nevertheless, the Okinawans demonstrate that consuming a plant-rich diet, lean protein sources, and healthy fats, appears to be a prudent choice, at least in adulthood. In particular, consuming more nutrient-dense but calorie poor vegetables, fruits and legumes will not only help most of us achieve a healthy weight, but increases our intake of health-enhancing phytonutrients. Understanding more about these nutritional phenomena, their biological pathways, and their relevance to human health, may lead to interventions that enable more of us to live longer, healthier and more productive lives.

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Key Points

- Older Okinawans consumed a diet consistent with mild caloric restriction, and rich in functional foods with CR-mimetic properties, especially sweet potatoes, turmeric and marine-based, carotenoid-rich foods.
- Older cohorts of Okinawans exhibit CR-like phenotypes (physically smaller, physiologically healthier, less age-related disease, longer healthspan, and longer average and maximum lifespan).
- The link between CR, CR-mimetic foods, and the good health of the Okinawans is supported by epidemiological and demographic data.
- Novel research is identifying biological pathways through which CR and CR mimetics act in model organisms of aging and humans. One of the most promising pathways is the insulin-IGF-1 signaling (IIS) pathway.
- FOXO3 is a major checkpoint gene in the IIS pathway and is one of only two genes consistently replicated for its effects on human longevity. This gene acts as a transcription factor that induces changes in gene expression in many target genes in response to biological stress. It is upregulated by CR and many CR-mimetic foods, increases stress resistance, and positively impacts healthspan and lifespan.