Published in final edited form as:
Exp Gerontol. 2013 October ; 48(10): 1003–1005. doi:10.1016/j.exger.2013.04.011.

Fasting or caloric restriction for Healthy Aging

Stephen Anton[*] and **Christiaan Leeuwenburgh**[*]
University of Florida, Department of Aging and Geriatric Research, Institute on Aging, Gainesville, FL, United States

Abstract

Aging is associated with a host of biological changes that contribute to a progressive decline in cognitive and physical function, ultimately leading to a loss of independence, and increased risk of mortality. To date, prolonged caloric restriction (i.e., a reduction in caloric intake without malnutrition) is the only non-genetic intervention that has consistently been found to extend both mean and maximal life span across a variety of species. Most individuals have difficulty sustaining prolonged caloric restriction, which has led to a search for alternative approaches that can produce similar to benefits as caloric restriction. A growing body of evidence indicates that fasting periods and intermittent fasting regimens in particular can trigger similar biological pathways as caloric restriction. For this reason, there is increasing scientific interest in further exploring the biological and metabolic effects of intermittent fasting periods, as well as whether long-term compliance may be improved by this type of dietary approach. This special will highlight the latest scientific findings related to the effects of both caloric restriction and intermittent fasting across various species including yeast, fruit flies, worms, rodents, primates, and humans. A specific emphasis is placed on translational research with findings from basic bench to bedside reviewed and practical clinical implications discussed.

Aging is associated with a host of biological changes that contribute to a progressive decline in cognitive and physical function, ultimately leading to a loss of independence, and increased risk of mortality. To date, caloric restriction (i.e., a reduction in caloric intake without malnutrition) is the only non-genetic intervention that has consistently been found to extend both mean and maximal life span across a variety of species. Key early studies in rodents revealed that mice fed 55–65% caloric restricted diets through their life exhibited a 35–65% greater mean and maximal lifespan than mice eating a non-purified ad libitum diet (Weindruch, 1996). Although attenuated, these effects remain present even when moderate caloric restriction (20–40%) is implemented in middle-aged mice (Weindruch et al., 2001). Importantly, prolonged caloric restriction has also been found to delay the onset of age-associated disease conditions such as cancer and diabetes in rodents (Weindruch et al., 2001) and in nonhuman primates (Colman et al., 2009). Thus, findings from animal studies, including recent primate studies, suggest prolonged caloric restriction has the potential to extend health-span and thereby increase quality of life.

In recent studies conducted in overweight humans, caloric restriction has been shown to improve a number of health outcomes including reducing several cardiac risk factors (Fontana et al., 2004, 2007; Lefevre et al., 2009), improving insulin-sensitivity (Larson-

[*]Corresponding authors at: Department of Aging and Geriatric Research, Institute on Aging, University of Florida, 1395 Center Drive, Rm. DG-22L, PO Box 100143, Gainesville, FL 32610, United States. Tel.: +1 352 273 5735; fax: +1 352 294 5058. santon@ufl.edu (S. Anton), cleeuwen@ufl.edu (C. Leeuwenburgh).

Conflict of interest
The authors have no conflicts of interests.

Meyer et al., 2006), and enhancing mitochondrial function (Civitarese et al., 2007). Additionally, prolonged caloric restriction has also been found to reduce oxidative damage to both DNA (Heilbronn and Ravussin, 2003; Heilbronn et al., 2006; Hofer et al., 2008) and RNA, as assessed through white blood cells (Hofer et al., 2008). Thus, findings of initial human clinical trials appear to support the promise of caloric restriction demonstrated in animal studies, at least in overweight adults.

Several different biological mechanisms may account for the increase in health span and longevity observed in response to caloric restriction in preclinical models. For example, aging is characterized by an exponential increase of oxidatively damaged proteins, and caloric restriction has been found to downregulate the expression of genes involved in oxidative stress and ameliorate oxidative damage in several different tissues (Hofer et al., 2009; Kayo et al., 2001; Lee et al., 1999; Marzetti et al., 2009; Opalach et al., 2010; Phillips and Leeuwenburgh, 2005). Additional biological changes associated with caloric restriction that may contribute to the observed increases in health span and longevity include enhanced cellular quality control through autophagy ("self-eating" of damaged organelles), improved function of the ubiquitin-proteosome system (UPS: removal damaged proteins), and the maintenance of a healthy population of mitochondria though biogenesis (generation of new mitochondria) (Aris et al., 2013; Dutta et al., 2012; Kayo et al., 2001; Lee et al., 1999; Rangaraju et al., 2009; Wohlgemuth et al., 2007, 2010). Despite these health promoting biological changes, most individuals have difficulty engaging in caloric restriction over the long-term (Scheen, 2008). Due to poor long-term compliance, an important area of study is whether compliance can be improved through the use of natural and/or pharmaceutical compounds that enhance satiety and/or whether similar biological effects may be achieved through alternative behavioral approaches.

One alternative dietary approach that may produce similar biological changes as caloric restriction that has received increasing interest from the scientific community is Intermittent Fasting. In contrast to traditional caloric restriction paradigms, food is not consumed during designated fasting time periods but is typically not restricted during designated feeding time periods. The length of the fasting time period can also vary but is frequently several continuous hours (see Review #1 by Chung). Evidence that this approach may have beneficial effects on longevity first appeared several decade ago (Carlson and Hoelzel, 1946). Since this time, a growing body of literature suggests that fasting periods and intermittent fasting regimens can trigger similar biological pathways as caloric restriction (i.e., increased autophagy and mitochondrial respiratory efficiency), which can result in a host of beneficial biological effects including increased circulation and cardiovascular disease protection, and modulation of reactive oxygen species and inflammatory cytokines (Lee and Longo, 2011), periods have also been shown to have antimutagenic, antibacterial, and anticarcinogenic effects (Lee and Longo, 2011).

In this issue, we include a total of 12 review articles, which examine the effects of caloric restriction on changes in biological and metabolic parameters across the lifespan. Within short-lived species (i.e., yeast, fruit flies, and worms), five reviews are included. Two of which focus on the link between dietary restriction, mitochondrial function, and chronological aging in yeast (i.e., *Saccharomyces cerevisiae*; see Kaeberlein et al., 2013) and *Caenorhabditis elegans* (see Park et al., 2013). We also include a review on the effects of resveratrol intake versus caloric restriction on biological and metabolic outcomes associated with aging. This comprehensive review includes data from rodents to humans (see Lam et al., 2013). Another review by Nelson et al., 2013 examines the genetic variation in responses to dietary restriction, as well the effects of methionine restriction on changes in regulation of oxidative stress and longevity (see Barja and Sanchez-Roman, 2013). For mammals, we include two reviews which focus on the effects of short-term caloric

restriction (see Mitchell and Robertson, 2013), and long-term dietary restriction in aging research (see Chung et al., 2013).

For clinical research, three reviews are included. The first of which reviews the controversies related to current lifestyle recommendations promoting diet-induced weight loss in obese adults 65 years and older (see Waters et al., 2013). The second review compares the effects of both food restriction and overeating on brain reward systems (see Avena et al., 2013). Finally, a third review by Shriner, 2013 revisits the concepts of detox and abstinence as they relate to food addition, as well as the effects of abstinence on clinical outcomes in metabolic pro-inflammatory conditions.

In this issue, we also include four organ specific reviews, which examine the effects of caloric restriction on eyes, hearing, nerves, and muscle. Specifically, a review by Hepple and Gouspillou, 2013 examines the facts and current controversies in our understanding of how caloric restriction impacts muscle mitochondrion. Another review by Notterpek and Lee, 2013 examines the endogenous protein quality control mechanisms through which caloric restriction supports peripheral nerve health. Next, a review by Han and Someya, 2013 examines the potential biological mechanisms through which caloric restriction impacts hearing including Sirt3 activation and modulation of glutathione levels. Finally, a review by Tsubota et al., 2013 examines the effects of both caloric restriction and calorie restriction mimetics on the prevention and treatment of age related eye disorders.

For original research, we include a total of five articles, which examine the biological effects of caloric restriction across short lived species, including yeast, worms, and fruit flies, as well as one article that examined the effects of fasting on indicators of muscle damage in humans (see Dannecker et al., 2013). For yeast, one original article is included, which examines the effects of dietary restriction on autophagy and leucine metabolism (see Aris et al., 2013), and another original article is included on the effects of short-term calorie and protein restriction on chemotoxicity and cancer progression (see Longo et al., 2013). We also include an original research article on the effects of high carbohydrate-low protein diets on lifespan in Drosophila (see Ja et al., 2013). Finally, we include a publication which incorporated some original data on the effects of caloric restriction on dehydroepian-drosterone sulfate (DHEAS) as an endocrine marker of aging in calorie restriction studies in primates (see Urbanski et al., 2013).

Future directions

A key issue for future research examining the effects of caloric restriction in humans is whether or not the promising findings from initial human trials translate to non-overweight individuals whose body mass index (BMI; kg/m^2) falls in the healthy range (i.e., BMI Range=20.0 – 24.9 kg/m^2). This possibility is currently being explored by the CALERIE Phase 2 study (Rochon et al., 2011). Specifically, the CALERIE Phase 2 study is examining the long-term effects of a 25% reduction of ad libitum energy intake in non-obese, middle-aged men and women (21–50 years) on markers of aging, cardiovascular disease risk, insulin sensitivity and secretion, immune function, neuroendocrine function, quality of life, and cognitive function (Rochon et al., 2011).

Although it is currently unknown if all humans benefit from engaging in caloric restriction, extensive research has shown that overweight and obese individuals receive numerous health benefits following weight loss achieved through caloric restriction (Nocera et al., 2011). Long-term compliance to conventional weight loss programs, however, is notoriously poor (Scheen, 2004, 2008), possibly due to internal feedback systems that defend against body weight change by signaling the body to increase food intake and decrease energy expenditure in response to caloric restriction (see Avena and Shriner et al.). The vast

majority of overweight individuals have difficulty sustaining a 20–40% reduction in calorie intake (Scheen, 2008), which appears to be necessary for the long-term maintenance of weight loss (Levine et al., 2007). Thus, an important area of study is whether long-term compliance can be improved either through novel behavioral approaches, such as intermittent fasting, or through the use of natural and pharmaceutical compounds that enhance satiety.

Another key issue is whether or not caloric restriction per se is needed to produce broad, systemic changes that can delay the onset of age-associated disease conditions or whether similar biological changes can be induced through intermittent fasting without caloric restriction (Arguin et al., 2012; Katare et al., 2009; Lee and Longo, 2011). A limitation of pre-clinical studies on fasting is that animals generally quickly consume all of the food that they are provided after a fasting regimen. This presents some concern as recent studies suggest that excessive caloric intake during a single feeding period can have negative health effects by dramatically increasing blood glucose levels, as well as corresponding production of reactive oxygen species and inflammatory cytokines (Ceriello, 2005a, 2005b). Noteworthy, these adverse physiological effects following ingestion of a single meal have been primarily documented in humans (Devaraj et al., 2008). Future research should explore the potential benefits of intermittent fasting approaches in humans, while also assessing the potential risks that may be associated with the increased caloric intake that typically occurs during non-fasting time periods. An alternative approach that has not been well explored to date is to pair caloric restriction approaches with intermittent fasting approaches, such that individuals would consume smaller portions with intermittent periods of fasting interspersed in their eating routine. In summary, a multitude of alternative dietary regimens (composition, frequency and duration)may hold promise in delivering similar benefits as caloric restriction, but these approaches need to be tested using various models of aging and ultimately in human clinical trials.

Acknowledgments

Support was provided by the University of Florida Claude D. Pepper Older Americans Independence Center (NIH/NIA P30AG028740) and the Clinical and Translational Science Institute (NIH/NCRR UL1TR000064). Stephen Anton is supported by a K23 AT004251-01A2, an Early Career Investigator Award from the American Heart Association (09CRP2390173), and Thomas H. Maren Foundation.

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