Published in final edited form as:

J Cardiopulm Rehabil Prev. 2013 ; 33(4): 201–208. doi:10.1097/HCR.0b013e318295019e.

Caloric Restriction:

IMPLICATIONS FOR HUMAN CARDIOMETABOLIC HEALTH

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Abstract

PURPOSE—While the impact of caloric restriction on human health is not fully understood, there is strong evidence to support further studies of its influence on cardiovascular health. The purpose of this review is to update the state of the science by examining the relevant literature regarding calorie restriction effects on aging and cardiovascular health and to discuss the possible role(s) of calorie restriction in preserving cardiovascular function in humans.

METHODS—For purpose of this review, we have defined calorie restriction as a reduction in energy intake well below the amount of calories that would be consumed *ad libitum* (10% in humans, 20% in animals). We examined the relevant literature on calorie restriction effects on longevity and cardiovascular health, with an emphasis on the state of the science regarding calorie restriction in humans. We have emphasized the importance of the preliminary and expected findings from the Comprehensive Assessment of the Long-term Effect of Reducing Intake of Energy (CALERIE) trial.

RESULTS—Evidence from animal studies and a limited number of human trials indicates that calorie restriction has the potential to both delay cardiac aging and help prevent atherosclerotic cardiovascular disease via beneficial effects on blood pressure, lipids, inflammatory processes, and potentially other mechanisms.

CONCLUSIONS—Based upon its known benefits to cardiometabolic health, including modest calorie restriction in a combined lifestyle program is likely to improve heart health and prevent subsequent cardiovascular events in overweight and obese individuals. Additional study is needed to further illuminate its long-term applicability for older adults and for those with significant comorbidities such as heart failure.

Keywords

calorie restriction; cardiovascular disease; health span; human cardiometabolic health; longevity; maximal life span; primary and secondary aging

The finding that restriction of energy (calorie) intake below the amount required for weight maintenance can slow the aging process and markedly extend lifespan was one of the most important health-related scientific discoveries of the 20th century. Scores of investigative

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The authors declare no conflicts of interest.

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teams, building on the original findings of McCay et al.¹ have since established that calorie restriction slows both primary aging (extends life span) and secondary aging (often referred to as health span) in a diverse array of organisms.² For the purpose of this review, primary aging refers to the rate at which the inevitable deterioration of cells and tissues occurs (independent of illness and environmental factors), while health span is determined by external influences, such as disease and detrimental lifestyle behaviors. Caloric restriction is specifically defined as a reduction in energy intake well below the amount of calories that would be consumed *ad libitum* (10% in human studies and usually 20% or higher in rodent species). There is growing evidence based on findings from these animal studies and a limited number of human trials, that calorie restriction has the potential to both delay aging of the cardiovascular system and help prevent atherosclerotic cardiovascular disease (CVD). The significance of this finding is obvious, since CVD remains the leading cause of mortality and one of the main causes for morbidity in older adults, despite tremendous overall progress in its prevention and treatment.

The purpose of this review is to examine the relevant literature on calorie restriction effects on longevity and cardiovascular health, providing both an update on the state of the science and a prediction for the future on the role of calorie restriction in preserving cardiovascular function in humans. A particular focus of this review will be on a newly completed study, the Comprehensive Assessment of the Long-term Effect of Reducing Intake of Energy or “CALERIE” trial, the anticipated findings of which will substantially elevate the state of the science regarding calorie restriction, cardiovascular health, and aging in humans.

CALERIE is the first randomized controlled study of the effects of calorie restriction on biomarkers of aging and longevity in human subjects.³ Phase 1 of CALERIE consisted of 3 independent, site-specific, short-term (6 to 12 months) studies; many of the results of these studies have already been published and are referenced subsequently in this review. Phase 2 of CALERIE (final subjects completed in early 2012) was a multicenter, single protocol trial that utilized intensive dietary and behavioral interventions focused on achieving and maintaining 25% calorie restriction throughout a 2-year intervention period. The subjects were healthy individuals (men aged 21-50 y and women aged 21-47 y) who were not obese (body mass index [BMI], 22.0 BMI<28.0 kg/m²). The results of Phase 2, which are due to be released within the year, will have important implications for our understanding of the impact of calorie restriction on human cardiovascular health as well as on aging and longevity.

Calorie restriction and Longevity: Impact and Mechanism

Based upon scores of studies conducted in animal models over the past 7 decades, the impact of calorie restriction on the aging process and longevity is well delineated.^{4,5} The ability to extend maximal lifespan using calorie restriction is highly reproducible; the extent of the effect depends on the model, but ranges as high as 60% in the most extensively studied (rodent) models (Figure 1).⁷ Careful, systematic study has revealed that the effects of calorie restriction are not due to reduced intakes of protein⁸ or micronutrients; calorie restriction studies typically use enriched diets to avoid any malnutrition. It is commonly accepted that reduction in energy (calorie) intake leads to a slowing of the aging process and a delay in the onset of chronic conditions commonly associated with the increasing morbidity and mortality of late life. Calorie restriction extends the lifespan of such diverse organisms as yeast, worms, flies, fish, and rodents^{9,10} and seems likely to have the same effects in nonhuman primates (rhesus monkeys).¹¹ In a 20-year longitudinal adult-onset calorie restriction study in rhesus macaques maintained at the Wisconsin National Primate Research Center, the incidence of aging-related deaths was lower in the calorie restriction group (50%) than in the *ad libitum* group (80%). The longevity effect was attributed to a

reduction in age-associated pathologies, including diabetes, cancer, cardiovascular disease, and brain atrophy.¹²

The original hypothesis¹ that calorie restriction increases lifespan by slowing the growth rate persisted for decades; however, it was dispelled in the 1980s by findings that calorie restriction effects could be demonstrated in mature animals.^{13,14} Theories proposing that the calorie restriction effect comes from lowering metabolic rate or reducing body fat have, for the most part, also been dispelled.^{15,16} Currently, the mechanisms proposed for life-prolongation by calorie restriction include an increase in apoptosis (thereby reducing the accumulation of damaged cells), an attenuation of oxidative damage, and a lowering of body temperature.⁹ However, as recently noted,¹⁷ it is likely that that multiple processes explain the anti-aging effects of calorie restriction. A broader framework for the effect mechanisms of caloric restriction has been proposed, one that includes processes that reduce the endogenous production of damaging agents (such as reactive oxygen species) as well as the effect of “hormesis”,^{18,19} which helps protect the organism from damaging agents and repair any resulting damage when it occurs.¹⁷

Despite intense interest in the implications of calorie restriction for human health and longevity,^{20,21} its effects on mortality in humans have not been well characterized, in part due to the obvious time demands of making observations over the duration of a human life time, and in part due to changes in adherence that would be evident in a randomized study design.

Observational studies of human subjects voluntarily undergoing calorie restriction,^{22,23} although providing some clues as to the long term effects of calorie restriction, are confounded by a number of other essential qualities that characterize the study population. Essentially all of the controlled, prospective studies of calorie restriction interventions in humans have been conducted in seriously overweight and obese (BMI ≥ 30 kg/m²) individuals over very short (usually 6 months) durations. This is not at all the same model as in animal studies; the animals are of normal weight and calorie restriction is continued for the duration of life (typically 2 to 3 years in a rat; the equivalent of decades in humans). Thus, most of what we know about the potential for calorie restriction to modify human health in nonobese subjects has been gleaned from observations in uncontrolled settings, namely an unplanned food shortage in Biosphere II²⁴ and studies of individuals who follow a calorie restriction diet independently from any controlled feeding trial.^{22,25} Additionally, there are a number of longitudinal population studies linking a low BMI with increased mortality from all causes, including cardiovascular disease. The oft-cited “U-shaped” relation between BMI and survival implies that being underweight as well as overweight is associated with a shortened lifespan²⁶ and this relation has been observed in a wide range of racial and ethnic groups.²⁷ However, the studies of BMI and mortality are not causal studies and they are subject to a number of confounders. Moreover, the quality of the diets of those with low BMIs is completely unknown and potentially lacking in important nutrients needed for long life.²⁶ With the completion of the second phase CALERIE, we will gain our first look at the results of a carefully controlled randomized trial of calorie restriction apart from any other nutrient restriction to document the effects on markers of primary and secondary aging in a nonobese human cohort over the course of 2 years.

Role of Calorie Restriction in Modification of Risk for Atherosclerotic Disease

The classic risk factors for atherosclerotic diseases (cardiovascular, cerebrovascular, and peripheral vascular) include dyslipidemias (high low density lipoprotein (LDL)-cholesterol, low high density lipoprotein (HDL)-cholesterol and elevated triglycerides), elevated blood

pressure, diabetes mellitus, and smoking. All but smoking are improved in response to calorie restriction in animal models, either directly or via the weight loss associated with it. While rodents do not provide a direct model for the type of CVD that occurs in humans, many of the effects of calorie restriction observed in rodents indicate a slowing of cardiovascular aging, such as a reduction in oxidative stress.² This effect of calorie restriction also occurs in nonhuman primates.²⁸

More recently, significant cardiovascular risk has been associated with the presence of the complex of cardiometabolic risks that constitute the metabolic syndrome: a combination of the elements of atherogenic dyslipidemia (elevated triglycerides in the presence of depressed HDL-cholesterol, or more specifically, the predominance of the small dense LDL and HDL particles), prehypertension to frank hypertension, elevated waist circumference (reflective of excess in visceral and subcutaneous abdominal adipose tissue) and elevated blood glucose (indicative of the late stages of progression to diabetes) to frank diabetes mellitus itself. Finally, cardiorespiratory fitness is now recognized as an independent predictor of cardiovascular risk independent of other risk factors.

In epidemiological studies, elevated serum cholesterol, both total and LDL-cholesterol, induce atherosclerosis in the absence of other risk factors. This is evident in human²⁹ and animal studies.³⁰ Furthermore, lowering cholesterol levels reduces cardiovascular disease mortality.³¹ Low HDL-cholesterol levels predispose to, and high HDL-cholesterol levels protect against, development of atherosclerosis.³¹ There is also evidence suggesting that high serum triglyceride levels may be atherogenic. Calorie restriction improves serum lipid profile, reducing the risk for atherosclerosis.³²⁻³⁵ To what extent calorie restriction modifies lipoprotein particle size and number is unknown.

Elevated blood pressure is a major risk factor for atherosclerosis, stroke, and renal failure. Furthermore, cardiovascular aging, resulting in a progressive increase in arterial stiffness, causes a progressive increase in systolic blood pressure, usually with no change or even a decrease in diastolic blood pressure in the elderly.³⁶ Data from studies on nonhuman primates suggest that calorie restriction lowers both systolic and diastolic blood pressure.³⁷ In humans, calorie restriction can also favorably effect blood pressure, as observed during food restriction for 2 years in the Biosphere 2 experiment.²⁴ Some of this may be mediated through modulation of the sympathetic-renin-angiotensin axis, the key members of which are being measured in CALERIE.

Chronic inflammation appears to increase with aging.^{38,39} The production of proinflammatory cytokines by mononuclear leukocytes in response to stimulation also increases with aging.³⁹ Calorie restriction reduces the acute release of proinflammatory cytokines in response to endotoxin and other stimuli in mice and monkeys, thus preventing excessive inflammatory responses and perhaps more important, protecting against the aging-related dysregulation of proinflammatory cytokine production.³⁹ Advanced glycosylation end-products (AGEs) also play an important role in the pathogenesis of aging and of cardiovascular and other diseases.⁴⁰ Some studies have observed that calorie restriction attenuates the accumulation of AGEs, including N-(carboxymethyl)lysine (CML) and pentosidine, major products of oxidative modification of glycated proteins.^{41,42}

Adipose tissue secretes a number of biologically active proteins, including leptin and adiponectin. Blood leptin increases with weight and fat gain and decreases with weight and fat loss. Leptin acutely increases fat utilization and suppresses appetite. However, chronic elevation of leptin concentrations cause marked resistance to the appetite suppressive and fat mobilizing effects of leptin.⁴³ Chronic elevation of leptin has a proinflammatory effect, and promotes smooth muscle cell proliferation and arterial stiffness.⁴³⁻⁴⁶ Adiponectin reverses

insulin resistance by increasing muscle and liver glucose uptake, decreasing hepatic glucose production and increasing insulin sensitivity.⁴⁷⁻⁵¹ An increase in circulating adiponectin concentration induced by calorie restriction could, thus, have an anti-aging effect by decreasing protein glycation and formation of AGE products.

Severe long-term calorie restriction has an extremely powerful protective effect against the risk of developing atherosclerotic cardiovascular disease (CVD). This effect is evidenced by very large decreases in blood pressure, serum total and LDL-cholesterol, triglycerides, low C-reactive protein, IL-6, TNF- α levels and a very large increase in HDL cholesterol (Table 1).^{10,22} This reduction in the risk of developing CVD is manifested by the absence of a thickening carotid artery intima-media over time and a complete absence of atherosclerotic plaques; this has been observed even in elderly calorie restricted individuals.²² In addition, left ventricular diastolic function was substantially better in the caloric restricted group (Table 2).²⁵ However, these findings were obtained on individuals who had been practicing long-term severe calorie restriction and were very thin (BMI values of 18 to 20 kg/m²). It is, therefore, not known whether the protective effects of calorie restriction against atherosclerotic CVD are mediated by a) persistent effects of weight or fat loss, b) the magnitude of the decrease in energy intake, or c) the final level of leanness, ie, percent fat mass and truncal fat mass. It is also not known to what extent the magnitude of the decrease in risk factors varies with the degree of calorie restriction. It is important to explore and evaluate the relative importance of these mechanisms. Having a combination of a low lean plus a low fat mass has been linked with increased mortality in patients with stable coronary heart disease; calorie restriction could result in such a body composition pattern.^{52,53}

Calorie Restriction Effects on the Neuroendocrine Axes and the Autonomic Nervous System

Plasma norepinephrine (NE) may play an important role in primary aging and is thought to mediate some calorie restriction effects on aging. NE concentration increases with advancing age and may lead to deterioration of cardiovascular and metabolic function.^{54,55} The increase in NE concentration is due to both increased secretion and decreased clearance, and it could be a potential marker for primary aging. Moreover, weight loss is associated with a decrease in plasma NE concentration.⁵⁶

The renin-angiotensin system (RAS) contributes to the pathogenesis of several human diseases, including hypertension, congestive heart failure, coronary artery disease, and diabetic nephropathy. There are several reports that the cardiovascular changes observed during aging are similar to those due to high blood pressure with respect to biochemical, mechanical, and electro-physiological properties of the cardiovascular system.^{57,58} In rats, both hypertension and advanced age⁵⁸ produce an increase in absolute and relative left ventricular weight and myocardial fibrosis.⁵⁹ The structure and function of the arterial wall also show similar modifications in hypertension and aging. The main vascular structural alteration is related to increased media thickness due to smooth muscle cell hypertrophy or hyperplasia and collagen accumulation,⁶⁰ resulting in increased stiffness.⁵⁹

The CALERIE trial Phase II provides excellent opportunities to elucidate the mechanisms by which calorie restriction mediates its protective effects against CVD because of a) the large subject group, b) the significant variation in the amounts of weight and body fat lost, c) the significant variation in the percent of calorie restriction achieved, and d) the significant variation in the final changes in body fat mass attained.

DISCUSSION

It should be apparent from the previous discussion that calorie restriction is not simply a means by which to lose weight or improve the nutrient intake. Benefits accrue with calorie restriction irrespective of the diet composition. Moreover, the calorie restriction regimen being discussed here stands in contrast to the modest reductions in caloric intake commonly taken on as part of a healthy lifestyle, although the latter is the type usually referred to as caloric restriction in the published literature. The calorie restriction effects referred to in this review constitute a significant reduction in calorie intake beyond that of *ad libitum* intake, and at a least 10% of that required for weight maintenance. Thus, calorie restriction is not a trivial intervention in humans and the duration over which it has to be continued in order to yield its benefits is unknown. It is therefore considered an experimental tool for studying the process of aging and its interaction with chronic disease. It is not the purpose of this review to recommend its implementation in the general population but rather to lay a foundation for interpreting the results of emerging findings from new studies in the human model. The CALERIE study was designed to test the health benefits of 2 years of this unique type of intensive calorie restriction; as its results emerge, so will answers to some of the most important questions posed about the long term benefits of calorie restriction, at least as they may be reflected by surrogate biological markers of aging.

The question of whether there is something special about calorie restriction itself, or whether the benefits of calorie restriction can be achieved by producing the same relative calorie deficit through exercise alone or in combination with calorie restriction is an open question and one of considerable interest. Most important, since the relative caloric deficit of significant calorie restriction (the difference between expenditure and intake) is so difficult to achieve, creating the same deficit by combining exercise and caloric restriction may be a very feasible and more beneficial method of achieving the same ends. Studies in rodent species would indicate that an equivalent energy deficit produced by exercise alone does not have the same effects on increasing maximal life span as does calorie restriction alone.⁶¹ This was initially addressed in a study in Phase I CALERIE where calorie restriction and a combined exercise and calorie restriction creating the same amount of relative caloric imbalance for 6 months led to equivalent amounts of reductions in serum triglycerides, C-reactive protein, and Factor VIIc, and increases in serum HDL-cholesterol.⁶² The effects of exercise alone versus calorie restriction alone (for up to 1 year) on surrogate markers of aging has only been addressed in one Phase I CALERIE Study. In this study, the calorie restriction alone failed to show any significant differences in effects on surrogate biological markers of aging, when compared with exercise of the same relative caloric deficit.^{63,64} Thus, the efficacy of exercise in combination or substitution for calorie restriction remains an open and significant one in humans.

Calorie Restriction and the Obesity Paradox in Older Individuals

That reducing calorie intake can promote more successful aging runs counter to traditional thinking about energy balance in later life. Weight loss in older adults has been thought to herald late life decline, being associated with chronic illness and cognitive impairments. Thus, until recently, the field of geriatrics has been more concerned about preventing weight loss in older adults than in promoting it.⁶⁵ Additionally, the observation of increased survival in heavier adults with inflammatory diseases characterized by wasting (cachexia), the so-called “reverse epidemiology” of obesity, has contributed to the idea that weight loss is undesirable in elders.⁶⁶ This paradoxical relation has been observed between obesity and a number of cardiovascular disorders. Further study is needed to delineate the best intervention for obese individuals who already have CVD, especially coronary heart disease and heart failure. It is likely that confounding factors account for at least some of these observed effects.⁶⁷

Nonetheless, the empirical evidence from studies of calorie restriction increasingly argues against a detrimental effect of caloric restriction, indicating that healthy adults may accrue a host of physiological benefits from the application of well-planned, moderate energy restriction. Further, whether the same benefits of calorie restriction are accrued in those in the latter stages of the life span versus earlier also remains a pertinent question. Studies in animal models are somewhat inconsistent on this issue, whereas some studies show that the benefits of calorie restriction can accrue even late in the life span,⁶⁸ others indicate that the earlier the age of institution the better in terms of calorie restriction benefits.^{69,70}

Application to Practice

Caloric restriction as a method for extending maximal lifespan in humans (as studied in CALERIE) is not yet ready for prime time; however, modest calorie restriction is a commonly used strategy in cardiac rehabilitation programs, especially when combined with exercise training. The benefits of modest calorie restriction, irrespective of the dietary composition, are such that it should continue to be part of a combined lifestyle program to improve cardiometabolic health. The results of the CALERIE trial and future studies will further illuminate the benefits and long-term applicability of caloric restriction for older adults and for those with significant cardiovascular disease.

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CONDENSED ABSTRACT

There is convincing evidence from animal models that caloric restriction benefits health by slowing the aging process and delaying the onset of age-associated chronic diseases, including cardiovascular disease. While the impact of calorie restriction on human health is not fully understood, there is strong evidence supporting the inclusion of modest calorie restriction in lifestyle programs targeting cardiovascular health.

Figure 1. Survival Curves for Rodents of Various Caloric Restriction Diets

This figure is typical of the survival patterns observed in rodent studies of calorie restriction. These curves are for the 4 treatment groups (Control and 85, 50, and 40 kcal/week) in the calorie restriction experiment of Weindruch et al.⁶ The symbols denote the observed mortality rates and the lines are the Gompertz maximum likelihood models. The figure was published in 2010 by Nature Education and is used with permission.

Table 1Effects of chronic caloric restriction on cardiovascular risk factors^a

Variable	Baseline	CR
BMI (kg/m ²)	24.5±2.6	19.5±2.1
T-cholesterol, mg/dL	194±45	157±38
LDL-C, mg/dL	122±36	86±17
TG, mg/dL	149±87	54±15
Systolic BP, mmHg	132±15	97±8
Diastolic BP, mmHg	80±11	59±5

^aData are mean±SD from 2 middle-aged subjects before and after 3-15 years of caloric restriction. Adapted from reference 22.

Abbreviations: CR, caloric restriction; BMI, body mass index; T, total; LDL-C, low density lipoprotein-cholesterol; TG, triglycerides; BP, blood pressure.

Table 2

Left ventricular diastolic function in caloric restricted and control subjects

Variable	CR (n=22)	Controls (n=25)	P-value
Age, y	52.7+/-11.9	53.4+/-6.5	NS
BMI, kg/m ²	19.7+/-1.8	27.0+/-2.1	.0001
Mean BP, mmHg	75+/- 8	99+/-7	.0001
Systolic shortening, %	34+/-6	36+/-6	NS
Peak E, cm/s	71+/-13	64+/-13	NS
Peak A, cm/s	46+/-9	53+/-10	.01
Atrial filling fraction	0.28+/-0.06	0.35+/-0.05	.0001
Deceleration time, ms	174+/-34	193+/-33	.01
E' lateral	14.3+/-3.0	10.2+/-2..8	.001
A' lateral	10.1+/-2.1	10.0+/-1.7	NS

Data are mean±SD. E' and A' were measured in only 12 caloric restricted and 23 control subjects. Adapted from reference 25.

Abbreviations: CR, calorie restriction; BMI, body mass index; BP, blood pressure.