

Aging, Adiposity, and Calorie Restriction

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AGING RESULTS IN A PROGRESSIVE decline in multiple organ systems, thus affecting reproductive, metabolic, physical, and cognitive function and, eventually, survival. Maximum life span, defined as the average life span of the longest-lived decile of a cohort,¹ is often used as a standard for evaluating the aging process, because valid biomarkers of physiological aging have not been identified.² The oldest documented person in recent history, Jeanne Louise Calment, died in 1997 at age 122 years, which represents the near-maximum human life span.³

Although it is unlikely that maximum human life span potential has changed much in recent history, life expectancy, defined as the age to which 50% of a population survive after birth, has markedly increased in most developed countries in the last century. Life expectancy from birth has increased from about 45 years in the early 1900s to about 75 years for men and 80 years for women today.⁴ This increase is due primarily to improved sanitation, better hygiene, reduced infant mortality, the development of antibiotics and vaccines, and better health care.⁵ In the last 15 years, there has been increasing interest in the potential therapeutic use of calorie restriction to obtain optimal health and increase life span in men and women, because calorie restriction has been shown to increase maximum life

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Context Excessive calorie intake and subsequent obesity increases the risk of developing chronic disease and decreases life expectancy. In rodent models, calorie restriction with adequate nutrient intake decreases the risk of developing chronic disease and extends maximum life span.

Objective To evaluate the physiological and clinical implications of calorie restriction with adequate nutrient intake.

Evidence Acquisition Search of PubMed (1966-December 2006) using terms encompassing various aspects of calorie restriction, dietary restriction, aging, longevity, life span, adiposity, and obesity; hand search of journals that focus on obesity, geriatrics, or aging; and search of reference lists of pertinent research and review articles and books. Reviewed reports (both basic science and clinical) included epidemiologic studies, case-control studies, and randomized controlled trials, with quality of data assessed by taking into account publication in a peer-reviewed journal, number of animals or individuals studied, objectivity of measurements, and techniques used to minimize bias.

Evidence Synthesis It is not known whether calorie restriction extends maximum life span or life expectancy in lean humans. However, calorie restriction in adult men and women causes many of the same metabolic adaptations that occur in calorie-restricted rodents and monkeys, including decreased metabolic, hormonal, and inflammatory risk factors for diabetes, cardiovascular disease, and possibly cancer. Excessive calorie restriction causes malnutrition and has adverse clinical effects.

Conclusions Calorie restriction in adult men and women causes beneficial metabolic, hormonal, and functional changes, but the precise amount of calorie intake or body fat mass associated with optimal health and maximum longevity in humans is not known. In addition, it is possible that even moderate calorie restriction may be harmful in specific patient populations, such as lean persons who have minimal amounts of body fat.

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span in many other species.⁶ In fact, societies, books, magazines, and Web sites are now available that are devoted to calorie restriction in humans.⁷

We performed a systematic review of the factors involved in the aging process and of the effect of calorie restriction (with adequate nutritional intake) on disease risk, maximum life span, and life expectancy. These factors have potentially important clinical and public health implications.

EVIDENCE ACQUISITION

Both basic science and clinical research studies were reviewed. PubMed

was searched from 1966 (volume 1) through December 2006, using various combinations of the key search terms *aging, geriatrics, longevity, lifespan, life expectancy, healthspan, calo-*

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rie restriction, food restriction, dietary restriction, energy restriction, adiposity, and obesity. Additional relevant articles were also found through a hand search of individual journals that focus on obesity, geriatrics, or aging and by identifying articles from the reference lists of research and review articles and books. The published clinical reports that we reviewed included epidemiologic studies, case-control studies, and randomized controlled trials. Although randomized controlled trials were considered to be the strongest evidence for evaluating the effect of an intervention, such studies were few, so the evidence was considered most compelling when there was consistency in results from multiple studies. Quality of data was assessed by taking into account publication in a peer-reviewed journal, number of animals or individuals studied, objectivity of measurements, and techniques used to minimize bias.

EVIDENCE SYNTHESIS

Mechanisms of Aging

Aging can be conceptualized as the result of 2 interactive and overlapping processes, known as primary and secondary aging.¹ However, this theory is not universally accepted because it is impossible to completely separate each factor. *Primary aging*, or “intrinsic senescence,” is the progressive deterioration in physical structure and biological function that occurs with advancing age alone, independent of other factors. For example, changes in body composition (ie, decreased bone mineral density, decreased muscle mass, and abdominal fat accumulation)⁸⁻¹⁰ and progressive decline of cardiac, pulmonary, renal, and immune function occur normally with increasing age.¹¹⁻¹³ *Secondary aging* is the accelerated deterioration in organ structure and function that is mediated by diseases, such as diabetes and hypertension, or by harmful environmental and lifestyle factors, such as excessive sun exposure or tobacco smoking.¹⁴⁻¹⁶

The precise biological and cellular mechanisms responsible for primary and secondary aging are not known but

likely involve a constellation of complex and interrelated factors, including (1) oxidative stress–induced protein and DNA damage¹⁷⁻¹⁹ in conjunction with inadequate DNA damage repair, as well as genetic instability of mitochondrial and nuclear genomes^{20,21}; (2) noninfectious chronic inflammation caused by increased adipokine and cytokine production²²; (3) alterations in fatty acid metabolism, including excessive free fatty acid release into plasma with subsequent tissue insulin resistance²³; (4) accumulation of cellular “garbage,” such as advanced glycation end products, amyloid, and proteins that interfere with normal cell function²⁴⁻²⁷; (5) sympathetic nervous system and angiotensin system activation as well as alterations in neuroendocrine systems²⁸⁻³⁰; and (6) loss of postmitotic cells, resulting in a decreased number of neurons and muscle cells as well as deterioration in structure and function of cells in all tissues and organs.³¹

Calorie Restriction and Aging in Animal Models

In 1935, McCay et al³² at Cornell University published the first scientific paper to report that calorie restriction in rats, when implemented after puberty, extended median and maximum life span and prevented or attenuated the severity of chronic disease. Subsequently, data have shown that calorie restriction, defined as a reduction in calorie intake below usual ad libitum intake without malnutrition, slows aging and increases maximum life span in different species, including yeasts, flies, worms, fish, and rodents.^{6,33,34} The age when calorie restriction is started, the severity of restriction, and the strain or genetic background of the animals determine the magnitude of life extension. In rodents, initiating a 30% to 60% reduction in calorie intake below usual ad libitum intake early in life (from shortly after weaning to age 6 months) caused a proportionate 30% to 60% increase in maximum life span, whereas a 44% reduction in calorie intake started in

adulthood (age \approx 12 months) extended maximum life span by only 10% to 20%.³⁵ The only mammals in which calorie restriction has clearly been shown to slow primary aging and extend maximum life span are rats and mice,^{6,33,34} with the exception of certain strains of captured wild mice.³⁶ Intermittent fasting (or alternate-day feeding) also increases resistance to toxicity and stress and prolongs maximum life span in rodents.³⁷

Data from studies conducted in laboratory rodents found that, in part, calorie restriction increases longevity by preventing or delaying the occurrence of chronic diseases, including diabetes, atherosclerosis, cardiomyopathy, autoimmune diseases, kidney and respiratory diseases, and cancer.^{6,32-35,37-39} In addition, calorie restriction decreases neurodegeneration in the brain and enhances neurogenesis in animal models of Alzheimer disease, Parkinson disease, Huntington disease, and stroke^{37,40} but could be detrimental in animal models of amyotrophic lateral sclerosis.⁴¹ However, the reduction of chronic diseases does not completely explain the increased life span and the preservation of function at more youthful-like states in calorie-restricted rodents; approximately one third of such rodents die without evidence of organ pathology.⁴² These data also support the notion that the common link between aging and chronic disease is not inevitable and that it is possible to live longer without experiencing a cumulative increase in serious morbidity and disability.

The mechanisms responsible for calorie restriction–mediated beneficial effects on primary aging observed in rodents probably involve the metabolic adaptations to restriction itself, including (1) decreased production of reactive oxygen species and modulation of the endogenous antioxidant systems, which decrease oxidative stress and free radical–induced tissue damage^{17,33,43-45}; (2) decreased circulating triiodothyronine (T₃) levels^{46,47} and sympathetic nervous system activity,⁴⁸ which cause a decrease in body tem-

perature and whole-body resting energy expenditure from baseline^{49,50}; (3) decreased plasma concentrations of inflammatory cytokines and a modest increase in levels of circulating cortisol, which result in a reduction in systemic inflammation,⁵¹⁻⁵⁵ (4) protection against aging-associated deterioration in immune function^{55,56}; and (5) increased expression of protein chaperones, such as heat shock protein 70, and of neurotrophic factors.³⁷ Calorie restriction also decreases the plasma concentrations of anabolic hormones and growth factors,⁵⁷⁻⁶⁰ which are involved in aging and tumorigenesis; life span is increased in mice deficient in growth hormone and in insulin-like growth factor 1 and its receptor.⁶¹⁻⁶³

In addition, calorie restriction simultaneously affects multiple processes that are involved in the genesis of aging, including enhanced DNA repair processes,⁶⁴ increased removal of damaged cellular proteins and oxidized lipids, decreased protein glycation and formation of advanced glycation end products,^{25,65,66} and decreased collagen cross-linking.⁴⁴ Many of the effects of calorie restriction are likely mediated by regulating gene expression through (1) up-regulation of genes involved in cellular repair and survival, stress resistance, and protection against oxidative damage; (2) down-regulation of genes involved in mediating inflammation; and (3) prevention of some changes in gene expression that occur with aging.⁶⁷⁻⁷⁰

Data from studies conducted in rodent models suggest that the effects of calorie restriction on maximum life span are mediated by calorie restriction itself and are not simply a result of leanness induced by such restriction. Maximum life span does not increase in male rats that maintain a low body fat mass by performing regular exercise on running wheels but does increase in sedentary male rats that are food-restricted to keep their body weights the same as those of the runners.^{71,72} Moreover, maximum life span is longer in calorie-restricted genetically obese (ob/ob) mice than in ad li-

bitum-fed, genetically normal, lean mice, even though body fat in the calorie-restricted ob/ob mouse is more than twice that of the genetically normal lean mouse.⁷³

It is not yet known whether calorie restriction affects primary aging and extends maximum life span in long-lived mammals. Two ongoing studies^{74,75} are evaluating the effect of such restriction on aging and maximum lifespan in rhesus monkeys, but it will probably take another 10 to 15 years before adequate data are available for reliable survival analyses. Nonetheless, the data currently available from these studies have shown that many of the metabolic, hormonal, anti-inflammatory, and body compositional changes that occur in calorie-restricted rodents also occur in calorie-restricted monkeys. These beneficial effects include (1) lower body weight and adiposity⁷⁶; (2) lower core body temperature and resting energy expenditure^{49,50}; (3) reduced T₃ concentration⁷⁷; (4) a blunted decline in concentration of plasma dehydroepiandrosterone sulfate⁷⁸; (5) improvement in risk factors for cardiometabolic disease, including blood pressure, serum lipid profile, serum glucose and insulin concentration, and insulin sensitivity⁷⁹⁻⁸¹; (6) decreased inflammatory markers, glycation products, and measures of oxidative stress^{82,83}; and (7) delayed immune senescence.⁸⁴

Calorie Restriction and Aging in Humans

It is difficult to determine whether calorie restriction has beneficial effects on longevity in humans because there are no validated biomarkers that can serve as surrogate markers of aging and because it is impractical to conduct randomized, diet-controlled, long-term survival studies in humans.² Nonetheless, data from epidemiologic studies suggest that calorie restriction can have beneficial effects on the factors involved in the pathogenesis of primary and secondary aging and life expectancy in humans. Food shortages during World War II in some European

countries were associated with a sharp decrease in coronary heart disease mortality, which increased again after the war ended.^{85,86} In addition, inhabitants of Okinawa island, who ate $\approx 30\%$ fewer calories than average Japanese residents, had $\approx 35\%$ lower rates of cardiovascular disease and cancer mortality than the average Japanese population and had one of the highest numbers of centenarians in the world.⁸⁷ However, these associations do not prove causality between decreased calorie intake and increased survival.

Data from recent studies reporting the effects of accidentally induced calorie restriction and voluntary self-imposed calorie restriction, as well as from short-term (6-12 months) randomized controlled trials examining calorie restriction as an intervention, can be used to help assess whether such restriction in humans causes the same biological adaptations that might be responsible for the slowed aging process observed in calorie-restricted rodents (TABLE). The 8 men and women who participated in Biosphere 2, an experiment that involved living in a completely closed self-sustaining ecological system, experienced a forced decrease in calorie intake for 18 months because of an unanticipated decrease in food availability. During this period, the participants consumed $\approx 22\%$ fewer calories (decrease from ≈ 2500 kcal/d to ≈ 1925 kcal/d) while sustaining high levels of physical activity required by their daily duties (≈ 70 -80 hours of work per week), which resulted in an approximately 17% decrease in body weight (body mass index [BMI] decrease from 23 to 19, measured as weight in kilograms divided by height in meters squared) and a marked reduction in metabolic risk factors for coronary heart disease, including plasma lipid profile and blood pressure.⁸⁹

Data from a series of studies conducted in members of the Calorie Restriction Society, which is a group that practices self-imposed calorie restriction in the belief that such restriction will extend their life span, have re-

cently been reported.⁹⁰⁻⁹² The calorie restriction group consisted of lean (mean BMI, 19.6 [SD, 1.6]) adult men and women (mean age, 51 [SD, 12] years; range, 35-82 years) who had been eating about 1800 kcal/d for an average of 6.5 years, which was \approx 30% fewer calories than age- and sex- matched individuals consuming a typical Western diet. Moreover, the composition of foods consumed by the calorie-restricted group differed from those consuming a Western diet. The calorie-restricted group ate a diet of nutrient-rich foods, such as vegetables, fruits, nuts, dairy products, egg whites, wheat

and soy proteins, and meat, which supplied more than 100% of the recommended daily intake for all essential nutrients; processed foods, which are rich in refined carbohydrates and partially hydrogenated oils, were avoided.⁹⁰ Compared with control individuals consuming a Western diet, the members of the Calorie Restriction Society showed many of the same alterations in metabolic and organ function previously reported in calorie-restricted rodents, including (1) low percentage of body fat, (2) low systolic and diastolic blood pressures, (3) markedly improved lipid profile, (4) increased

insulin sensitivity, (5) low plasma concentrations of inflammatory markers, (6) low levels of circulating growth factors, and (7) low serum concentrations of T_3 .⁹⁰⁻⁹² In addition, left ventricular diastolic function (ie, parameters of viscoelasticity and stiffness) in calorie-restricted individuals was similar to function in those who were approximately 16 years younger⁹² and is consistent with the beneficial cardiac effects of calorie restriction observed in mice.⁹⁹

Several randomized, controlled intervention trials have evaluated the effect of calorie restriction on aging-

Table. Effects of Long-term Calorie Restriction in Humans

Source	Study Type	Initial Weight Status*	No. With Calorie Restriction	Decrease in Calorie Intake, %	Duration of Calorie Restriction	Findings in Calorie-Restricted Group
Keys et al, ⁸⁸ 1950	Longitudinal	Lean	36	45	6 mo	Decreased body fat, blood pressure, T_3 levels, resting heart rate, and resting energy expenditure; improved lipid profile; anemia, muscle wasting, neurologic deficits, edema, weakness, dizziness, lethargy, irritability, depression
Walford et al, ⁸⁹ 2002	Longitudinal	Lean	8	\approx 22†	18 mo	Decreased BMI, blood pressure, WBC count, and levels of insulin, glucose, LDL-C, HDL-C, triglycerides, uric acid, and T_3
Fontana et al, ⁹⁰ 2004	Cross-sectional	Lean	18	\approx 30	\approx 7 y	Decreased body fat, blood pressure, carotid artery intima-media thickness, and levels of LDL-C, triglycerides, glucose, insulin, CRP, and PDGF; increased HDL-C levels
Fontana et al, ⁹¹ 2006	Cross-sectional	Lean	28	\approx 30	\approx 7 y	Decreased T_3 levels; unchanged levels of TSH and T_4
Meyer et al, ⁹² 2006	Cross-sectional	Lean	25	\approx 30	\approx 7 y	Improved left ventricular diastolic function; decreased levels of TNF- α and TGF- β
Heilbronn et al, ⁹³ 2006	RCT	Lean and overweight	12	25	6 mo	Decreased body fat, body temperature, 24-h energy expenditure, and levels of insulin, T_3 , and DNA damage marker; unchanged levels of DHEAS
Larson-Meyer et al, ⁹⁴ 2006	RCT	Lean and overweight	12	25	6 mo	Decreased visceral adipose tissue, subcutaneous adipose tissue, and fat-cell size
Racette et al, ⁹⁵ 2006	RCT	Lean and overweight	19	20	12 mo	Decreased body fat, visceral adipose tissue, subcutaneous adipose tissue, and fat-free mass
Villareal et al, ⁹⁶ 2006	RCT	Lean and overweight	18	20	12 mo	Decreased leptin levels and bone mineral densities at spine and hip; increased CTX levels
Weiss et al, ⁹⁷ 2006	RCT	Lean and overweight	18	20	12 mo	Decreased TNF- α /adiponectin ratio and levels of insulin and glucose; increased ISI and adiponectin levels
Weiss et al, ⁹⁸ 2006	RCT	Lean and overweight	18	20	12 mo	Decreased muscle mass and absolute physical work capacity

Abbreviations: BMI, body mass index; CRP, C-reactive protein; CTX, C-telopeptide of type I collagen; DHEAS, dehydroepiandrosterone sulfate; HDL-C, high-density lipoprotein cholesterol; ISI, Matsuda insulin sensitivity index; LDL-C, low-density lipoprotein cholesterol; PDGF, platelet-derived growth factor; RCT, randomized controlled trial; T_3 , triiodothyronine; T_4 , thyroxine; TGF- β , transforming growth factor β ; TNF- α , tumor necrosis factor α ; TSH, thyrotropin; WBC, white blood cell.

*Based on BMI.

†Weight loss was caused by reduced energy intake and increased energy expenditure (\approx 70-80 hours of work per week).

related variables in nonobese (lean and overweight) adults. The results from 1 study found that a 25% reduction in calorie intake for 6 months decreased visceral fat mass, insulin resistance, body temperature, metabolic rate, and levels of 1 marker of oxidative stress.^{93,94,100} Another trial demonstrated that a 20% reduction in calorie intake for 12 months reduced visceral fat mass, decreased levels of circulating inflammatory markers, and improved insulin sensitivity.^{95,97} However, the data from this study also found that calorie restriction decreased bone mass as well as lower extremity muscle mass and strength.^{96,98}

Despite many similarities in the metabolic adaptation to calorie restriction observed in rodents and humans, it is not known if such restriction affects maximum life span in humans. In fact, it has been proposed that calorie restriction can only minimally extend maximum life span in human and non-human primates because of differences in “metabolic stability,” “evolutionary entropy,” and “dietary reaction norms” between species.^{101,102} These hypotheses use evolutionary principles to evaluate the potential relationship between calorie intake and longevity in different species, based on reproductive function, cellular regulatory networks, and genotypic-phenotypic population changes caused by mutation and selection.

Calorie Restriction and Obesity

Obesity is associated with impaired function of most organ systems, serious medical diseases, and premature mortality.¹⁰³⁻¹⁰⁵ The worldwide prevalence of obesity has increased markedly over the last several decades. In the United States, approximately 30% of adults and 15% of children and adolescents are obese, defined as a BMI of 30 or greater for adults and a BMI in the 95th or greater percentile (age- and sex-specific) for children and adolescents.¹⁰⁶

Weight loss, induced by a negative energy balance, simultaneously improves multiple metabolic risk factors for cardiovascular disease and other

medical abnormalities associated with obesity.¹⁰⁷ In addition, data from several recent studies suggest that bariatric surgery–induced calorie restriction, which causes sustained long-term weight loss, can decrease mortality rate in extremely obese patients,¹⁰⁸⁻¹¹⁰ presumably by improving obesity-related medical complications. In contrast, removal of large amounts of subcutaneous body fat by liposuction does not improve insulin sensitivity or other metabolic risk factors for cardiovascular disease.¹¹¹ Therefore, calorie restriction is the cornerstone of obesity therapy, whereas reducing adipose tissue mass by surgical aspiration does not provide metabolic benefits.

Unhealthy Excessive Calorie Restriction

Excessive calorie restriction can be defined as a decrease in calorie intake that has deleterious effects on organ function and health. The adverse effects of extreme restriction in humans are known. The “Minnesota Starvation Experiment,” conducted between 1944 and 1945 in World War II conscientious objectors, provides the earliest systematic evaluation of the effect of severe calorie restriction in normal-weight individuals.⁸⁸ In this study, baseline calorie intake was reduced by 45% for 24 weeks in lean men. These men exhibited many of the potentially beneficial metabolic adaptations of calorie restriction observed in later studies conducted in both animals and humans, such as decreased body fat, blood pressure, improved lipid profile, low serum T₃ concentration, and decreased resting heart rate and whole-body resting energy expenditure. However, this amount of calorie restriction also had serious deleterious effects, including anemia, muscle wasting, neurologic deficits, lower extremity edema, weakness, dizziness, lethargy, irritability, and depression.

Additional clinical effects of excessive calorie restriction are often found in patients who have anorexia nervosa. These patients have a distorted body image, which leads to excessive

calorie restriction and severe malnutrition, manifested by impaired regulation of body temperature and by adverse changes in the skin (dry, wrinkled, atrophic), hair (thin, sparse, easily pulled out), bone (osteoporosis), bone marrow (suppressed red blood cell and white blood cell production, leading to anemia, leukopenia, and lymphocytopenia), cardiovascular system (decreased cardiac muscle mass, cardiac output, bradycardia, and hypotension), lungs (decrease in vital capacity, tidal volume, and minute ventilation), immune system (atrophy of lymphoid tissues, impaired cell-mediated immunity, and increased risk of infection), and reproductive system (amenorrhea, infertility).^{112,113}

It is not possible to determine a safe threshold of calorie restriction for all persons because of the influence of many different factors, such as initial body composition, daily energy expenditure, and duration of calorie restriction. Moreover, it is possible that a specific reduction in calorie intake will simultaneously benefit some organ systems (eg, cardiovascular) and harm others (eg, bone).^{92,96} The data from the “Minnesota Starvation Experiment” demonstrate that a 45% reduction in usual energy intake for 24 weeks is harmful in lean men.⁸⁸ It is likely that less severe calorie restriction would also have adverse effects if continued for a longer period in lean young and elderly individuals. Assessment of BMI can be used as one parameter to evaluate the safety of calorie restriction because of the effect of restriction on BMI and the relationship between BMI and clinical outcome. A BMI less than 18.5 is associated with an increase in mortality rate in young, middle-aged, and older adults,^{114,115} and death from starvation often occurs at a BMI of 13 in men and 11 in women.¹¹⁶

Optimal Health

“Optimal health” can be defined as the state in which there is the highest possible attainment of physical, mental, and social well-being and the lowest risk of developing future diseases. However, de-

termining whether health status is optimal is difficult because of the complexity of reliably predicting health outcomes. In a clinical setting, easily accessible biomarkers are often used to determine disease risk. For example, increased fasting plasma glucose concentration, increased concentration of serum low-density lipoprotein cholesterol, and increased blood pressure are associated with an increased risk of cardiovascular disease. Although the relationship between biomarkers and disease is often a continuum, cut points have been established to identify individuals at increased risk. Recently, data from several large intervention studies suggest that the thresholds for many of the major risk factors for coronary heart disease should be lowered. Therefore, optimal health is associated with a lower level of systolic/diastolic blood pressure (<115/75 mm Hg vs a previous threshold of 140/80 mm Hg),^{117,118} lower concentration of plasma low-density lipoprotein cholesterol (50-70 mg/dL vs <100 mg/dL [1.3-1.8 mmol/L vs <2.6 mmol/L]),^{119,120} and lower concentration of fasting plasma glucose (75 mg/dL vs <100 mg/dL [4.2 mmol/L vs <5.6 mmol/L])^{121,122} than the current "normal" cut points.

Data from large population studies suggest that lifestyle factors, such as sedentary lifestyle, dietary intake, and adiposity, are responsible for up to 70% of chronic disease and are a major contributor to reduced longevity.^{123,124} However, the precise amount of calorie intake or body fat mass associated with "optimal health" is not known. The World Health Organization, the National Institutes of Health, and other groups have proposed that a BMI between 18.5 to 24.9 is normal, because BMI values below or above this range increase the risk for premature mortality.¹²⁵⁻¹²⁷ Data from epidemiologic studies that evaluated the relationship between BMI and risk of type 2 diabetes¹²⁸ and from studies of individuals who have undertaken long-term calorie restriction⁹⁰⁻⁹² suggest that a BMI at the low end of normal, ≈ 20 , is associated with optimal

metabolic and cardiovascular health. This value correlates with an average percentage body fat of $\approx 10\%$ in men and $\approx 25\%$ in women.¹²⁹ However, the amount of adiposity and BMI values associated with optimal health in men and women will vary depending on genetic and environmental influences, body fat distribution, age, and racial/ethnic background.¹³⁰⁻¹³²

Calorie-Restriction Mimetics

Even if calorie restriction is shown to increase life expectancy and maximum life span in humans, it is unlikely that such restriction will be widely adopted because of the difficulty in maintaining long-term calorie restriction (ie, low calorie intake) in modern society. Therefore, there has been an increased interest in developing pharmacological agents that act as "calorie-restriction mimetics." Such agents could provide the beneficial metabolic, hormonal, and physiological effects of calorie restriction without having to alter dietary intake or experience any potential adverse consequences of excessive restriction.

Several compounds have been proposed as potential calorie-restriction mimetics, such as plant-derived polyphenolic molecules (eg, resveratrol, quercetin, butein, piceatannol), insulin-action enhancers (eg, metformin), or pharmacological agents that inhibit glycolysis (eg, 2-deoxyglucose).¹³³ Resveratrol, which is present in grapes, peanuts, and several other plants, is a potent inducer of the sirtuin/Sir2 family of NAD⁺-dependent deacetylases. *SIRT1*, one of the 7 mammalian sirtuin genes, regulates several biological functions, including cell survival, which has led to the theory that sirtuins mediate some of the effects of calorie restriction in mammals.^{134,135} Treatment with metformin, a biguanide oral hypoglycemic agent, can decrease the risk of developing diabetes in persons with impaired oral glucose tolerance and of developing cancer in patients with diabetes, and causes some of the same changes in gene expression observed

in calorie-restricted mice.¹³⁶⁻¹³⁸ Dietary supplementation with a glycolytic inhibitor, 2-deoxy-D-glucose, decreases serum glucose and insulin concentrations, resting heart rate, and blood pressure, and improves the response to neuroendocrine stress in rats.^{133,139} However, additional studies are needed to determine whether these and other candidate calorie-restriction mimetics actually affect life expectancy in humans.

CONCLUSIONS

Calorie intake is an important determinant of health. Inadequate and excessive energy intakes represent different forms of malnutrition that lead to unfavorable changes in body composition, organ dysfunction, and premature mortality. The precise calorie intake needed for optimal health and function likely varies for each individual, depending on genetic background, age, energy expenditure, and diet composition. Moreover, the optimal calorie intake needed to slow the aging process is not known. However, the available data support the notion that calorie restriction with adequate nutrient intake in humans causes many of the same metabolic adaptations and reduction of multiple chronic disease risk factors that occur in calorie-restricted animal models, even when restriction is started in midlife. Therefore, even if calorie restriction does not prolong maximum life span, it could increase life expectancy and the quality of late life by reducing the burden of chronic disease. However, any amount of calorie restriction could be harmful in specific populations, such as lean persons, who have minimal body fat stores (eg, BMI <18.5 in adults). Additional studies are needed to identify the molecular and cellular mechanisms responsible for the therapeutic effects of calorie restriction and to identify reliable and sensitive markers of aging to facilitate evaluating the effect of calorie restriction in randomized controlled clinical trials.

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In a very real sense, people who have read good literature have lived more than people who cannot or will not read. It is not true that we can have only one life to live. If we can read, we can live as many lives and as many kinds of lives as we wish.

—S. I. Hayakawa (1906-1992)