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Review article

Caloric restriction *versus* drug therapy to delay the onset of aging diseases and extend life

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Abstract

There are two firmly established methods of prolonging life. Calorie restriction (CR) using nutrient-rich diets to prolong life in lower animals, and life saving medications in humans to delay the development of the major diseases of middle and old age. These two approaches have different mechanisms of action. In rats, CR at 40% below *ad libitum* intake begun soon after weaning and continued until death, reduces body weight by about 40% and increases lifespan. There have been no lifelong CR studies performed on humans. However, in healthy adult human subjects about 20% CR over a period of 2–15 years, lowers body weight by about 20% and decreases body mass index (BMI) to about 19. This CR treatment in humans reduces blood pressure and blood cholesterol to a similar extent as the specific drugs used to delay the onset of vascular disease and so extend human life. These same drugs may act by mechanisms that overlap with some of the mechanisms of CR in retarding these pathologies and thus may have similar antiaging and life prolonging actions. Such drugs may be regarded as CR mimetics which inhibit the development of certain life shortening diseases, without the need to lower calorie intake. In developed countries, better medical care, drug therapy, vaccinations, and other public health measures have extended human life by about 30 years during the 20th century without recourse to CR, which is so effective in the rat. The percentage gain in human life expectancy during the 20th century is twice that achieved by CR in rat survival. However, rat longevity studies now use specific pathogen-free animals and start CR after weaning or later, thereby excluding deaths from infectious diseases and those associated with birth and early life. There is a need to develop CR mimetics which can delay the development of life-threatening diseases in humans. In the 21st century due to the human epidemic of overeating with a sedentary lifestyle, it may necessary to utilize CR to counter the aging effects of overweight. Since the greatest life-extending effects of CR in the rodent occur when started early in life, long-term antiaging therapy in humans should be initiated soon after maturity, when physiological systems have developed optimally.

Introduction

In the rat 40% calorie restriction (CR) continued from soon after weaning until old age inhibits almost all physiologic processes of aging, delays the onset of most pathology, and extends both the mean and maximum life spans by about 20% to 40% (McCay et al. 1935; Weindruch and Walford 1988a; Weindruch and Sohal 1997; Masoro 2002a; Lane et al. 2002; Heilbronn and Ravussen 2003). The life-prolonging action of dietary restriction is a robust effect, first shown in the critical studies of McCay et al. (1935), and repeatedly demonstrated in a number of lower animal species in many laboratories. CR produces a

smaller increase in lifespan when started in later life (Weindruch and Walford 1988a; Weindruch and Sohal 1997). Histopathologic studies in the male Sprague–Dawley rat have shown that lifelong 45% dietary restriction will delay the onset of four major diseases of old age (nephrosis, periarteritis, myocardial degeneration, and skeletal muscle degeneration) by the equivalent of 30–80 human years (Berg and Simms 1965). The dietary restricted rats remained free of disease much longer than the fully fed rats due to the later onset of disease. It is believed that CR will also delay disease onset and prolong life in human subjects, but this has not yet been investigated (Weindruch and Walford 1988b; Everitt 2004). However, during the last three decades of the 20th century, human longevity has been increased by about 10 years mainly due to the use of drugs that lower blood pressure and blood cholesterol, causing significant reduction in deaths from cardiovascular disease (Kannel and Thom 1984; Stamler 1985; Sytkowski et al. 1990). It is suggested that the life extending effects of specific drugs and calorie restriction may have some overlapping mechanisms.

Calorie restriction, cardiovascular disease and median or average lifespan

Due to similarities in physiology, nonhuman primates are being used as a first step in the study of the long-term effects of CR on human aging and median or average lifespan (Lane et al. 2002). At the National Institute on Aging, rhesus monkeys were placed on a nutrient dense 30% CR diet starting in 1987 (Ingram et al. 1990). After 12 years of CR, these monkeys showed reductions in the risk factors for cardiovascular disease (blood pressure and blood cholesterol) and diabetes mellitus (blood glucose and plasma insulin) (Lane et al. 1999, 2000). The CR monkeys in middle age were healthier and had about half the mortality of fully fed controls of the same age (Lane et al. 2002). In a separate study Bodkin and colleagues (Bodkin et al. 2003) reported that over a 25-year period eight dietary restricted monkeys had a median survival of 32 years compared with 25 years in 109 *ad libitum* fed controls. Although a number of caveats have been raised regarding the latter analysis (Lane et al. 2004), CR in a nonhuman primate has been able to reduce the risks for vascular disease and diabetes mellitus, and also decrease mortality risk.

In healthy human subjects long-term CR has been shown to reduce the risk factors for both cardiovascular disease and diabetes mellitus (Walford et al. 1992, 2002; Fontana et al. 2004; Velthuis-te Wierik et al. 1994). When eight healthy, nonobese, nonsmoking, adult subjects aged 27–67 years were sealed in Biosphere 2 in Arizona and placed on a nutrient dense 20% CR diet for 2 years, they developed 20% or more reductions in body weight, blood pressure, blood cholesterol, blood triglycerides, fasting blood glucose and insulin (Walford et al. 2002). These findings were confirmed and extended in a more recent study (Fontana et al. 2004) of Self Imposed CR over 3–15 years in 18 healthy subjects aged 35–82 years. In addition, the CR group had 40% lower values of carotid artery intima-medial thickness, showing that CR protects against atherosclerosis (Fontana et al. 2004). Another factor in atherosclerosis, the level of inflammation as measured by C-reactive protein, was extremely low in this CR study (Fontana et al. 2004). In both of these CR studies, the body mass index (BMI) was reduced to about 19. In general, the physiological and biochemical changes produced by CR in humans are similar to those reported in rhesus monkeys living on equivalent diets which reduce mortality (Lane et al. 1999) and in rodent CR studies which prolong life (Masoro 1995). In the 1950s a 3-year survival study of 120 men and women aged 65 or more years in a Spanish nursing home subjected to a 35% reduction in calories revealed a significant decrease in the number of sick days in CR patients, but failed to extend life (Vallejo 1957; Stunkard 1976).

Calorie restriction, drugs and cardiovascular disease

In recent decades human longevity has been increased by the use of drugs that lower blood pressure and blood cholesterol, thereby reducing deaths from cardiovascular disease (Kannel and Thom 1984; Stamler 1985; Sytkowski et al. 1990). Reduced smoking also contributed to the decline in mortality (Kannel and Thom 1984), since long-term smoking can shorten life by up to 10 years (Doll et al. 2004). The Polypill is a hypothetical combination of three antihypertensive agents at half dose, plus a statin, aspirin, and folic acid that has been proposed as a broad spectrum agent for the prevention of cardio-

vascular disease in people over the age of 55 years (Wald and Law 2003; Law et al. 2003a, b). Wald and Law (2003) estimate that by taking the Polypill, 12 years of extra life will be gained by men and women aged 55 years who have no known vascular disease. The magnitude of the reductions in cardiovascular disease risk factors such as systolic and diastolic blood pressures and blood lipids (both total and LDL cholesterol) is similar in the Self Imposed CR project, the CR Biosphere 2 study, and the proposed Polypill (see Table 1). There is emerging evidence of overlap between the mechanisms by which CR and the Polypill may reduce cardiovascular risk factors. Energy restriction resulting in even modest weight loss suppresses endogenous cholesterol synthesis (Di Buono et al. 1999) as does 3-hydroxy-3-methyl glutaryl coenzyme A (HMG CoA) reductase inhibition. Recently it has been shown that weight loss correlates with reduction in angiotensin converting enzyme (ACE) activity and reduced angiotensinogen, renin and aldosterone levels (Engeli et al. 2005) suggesting a parallel between the mechanisms of CR and ACE inhibitors in blood pressure reduction. Furthermore, the actions of medications used to control vascular risk factors, for example, HMG CoA reductase inhibitors (Wainwright 2005) and ACE inhibitors (Savo et al. 2003) have antiaging effects beyond blocking their respective target enzymes. The broad antiaging actions of these drugs increase the probability of overlap with actions of CR.

In rhesus monkeys 30% CR also has similar effects (Lane et al. 1999, 2000; Table 1) to those seen in humans. Both the Self Imposed CR and the Biosphere intervention led to reductions in other cardiovascular risk factors such as body weight, BMI, fasting blood glucose, insulin, and triglycerides, which are unlikely to occur with the Polypill, although other drugs will produce these changes. The additional effects of the Polypill on homocysteine and platelets were not examined in the Self Imposed and Biosphere subjects, nor in rhesus monkeys. Also the decreases in the C-reactive protein and carotid artery intima-medial thickness were investigated only in the Self Imposed CR study. The overlap between the effects of the Polypill and CR implies a significant role for vascular disease in aging and survival.

Moderately elevated blood glucose is a risk factor for cardiovascular disease (Phillips et al. 2003) and also for diabetes mellitus, which is becoming a major disease of old age (Morley 2000). The main risk factors for diabetes mellitus are raised fasting blood glucose and high blood insulin. In healthy adult humans CR reduced fasting blood glucose by 15% and 21%, respectively, in the Self-Imposed and the Biosphere studies. There were much greater reductions in fasting insulin of 72% and 42%, respectively, in these studies on humans, consistent with increased insulin sensitivity. In rhesus monkeys CR also reduced blood glucose and insulin levels (Lane et al. 1995, 1999, 2000; Hansen and Bodkin 1993; Table 1), and similar reductions are seen in CR rats

Table 1. Comparison of the reductions in cardiovascular risk factors produced by CR Self-Imposed, by 20% CR in Biosphere 2, by drugs using the theoretical Polypill in humans, and by 30% in rhesus monkeys.

Cardiovascular risk factors	CR humans Self-Imposed	20% CR humans Biosphere 2	Drugs humans Polypill	30% CR rhesus monkeys
Systolic BP (mmHg)	30	20	20	10
Diastolic BP (mmHg)	18	23	11	20
Total cholesterol (mg/dl)	47	67	85	15
LDL cholesterol (mg/dl)	41	55	70	?
Triglycerides (mg/dl)	99	50	?	51
Body weight (% decrease)	26	17	0	22
Fasting glucose (% decrease)	15	21	?	25
Fasting insulin (% decrease)	72	42	?	50
Homocysteine (μmol/l)	?	?	3	?

Data for the Self Imposed CR study are taken from Fontana et al. (2004).
Data for the Biosphere 2 study are taken from Walford et al. (2002).
Data for the Polypill study are taken from Wald and Law (2003), Law et al. (2003a, b).
Data for the rhesus monkey studies are taken from Lane et al. (1999, 2000).
?: no data available.

(Masoro et al. 1992). Blood glucose control is influenced not only by the calorie intake but also by the glycemic index of the food consumed (Willett et al. 2002; Brand-Miller et al. 2002). Poor blood glucose control leads to microvascular disease of retina and kidneys plus increased risk of macrovascular disease, including cardiovascular, cerebrovascular, peripheral vascular disease and vascular dementia (Morley 2000). In patients with impaired glucose tolerance, diabetes can be prevented by diet, with or without exercise (Willett et al. 2002; Pan et al. 1997; Tuomiolehto et al. 2001). Drug therapy is less effective than lifestyle changes (Diabetes Prevention Program Research Group 2002). Antidiabetic drugs are reported to have antiaging and life-prolonging actions in rodents (Anisimov et al. 2003a).

Dietary energy intake, health care and median or average lifespan

In the United States calorie intake per capita per day has increased from 2,883 in 1961 to 3,772 in 2001 (OECD Health Data 2004), a gain of 30%. In Japan, which has the greatest life expectancy, calorie intake increased from 2,468 to 2,762 over this period (OECD Health Data 2004), an increase of 12%. An excessive energy intake coupled with a sedentary lifestyle in many countries has led to an epidemic of overweight and obesity that is creating major health problems worldwide (Cameron et al. 2003; Must et al. 1999). Insulin resistance is often seen in obese subjects and is a contributing factor to the excessive weight gain (Reaven 1995). Obesity is regarded as a chronic disease (Fujioka 2002; Must et al. 1999), which increases the risk of type 2 diabetes, hypertension, coronary heart disease, cancers of the endometrium, breast, prostate and colon and is associated with increased mortality. The decrease in life expectancy at age 40 is 3 years for the overweight with a BMI of 25–30, and 7 years for the obese man or woman with a BMI of >30 (Peeters et al. 2003). For white men aged 20–30 years with severe obesity (BMI > 45), the maximum years lost is 13 and for white women 8 years (Fontaine et al. 2003). This epidemic of overweight, which is life shortening, will counter the gains made by the medical profession in prolonging life with medication and other therapies. The prevention of obesity (BMI > 30) in middle age by reduced energy intake would be expected to extend life by about 7 years (Peeters et al. 2003).

As previously mentioned, many rat studies have repeatedly shown that a long-term reduction of 40% in energy intake, results in a gain of about 20 to 40% in mean life duration (Weindruch and Walford 1988a; Weindruch and Sohal 1997; Masoro 2002a; Yu et al. 1982). However, in human populations in 1996, the Okinawans in Japan were consuming 40% fewer calories than the Americans, but lived only 4 years longer (Willcox et al. 2001), a gain of about 5%. This is probably because medicine and public health had already achieved a large increase in life expectancy during the 20th century without the help of CR (Guyer et al. 2000), although differences in other lifestyle and genetic factors may be contributing (Everitt 2004; Willcox et al. 2001). Human life expectancy at birth in 10 developed countries during the 20th century has increased on average by about 30 years (Cooper et al. 2002; Table 2) from about 50 years in 1900 (United Nations 1957) to about 80 years in 2002 (World Health Organization 2003), due to improvements in public health and medical care (Guyer et al. 2000; Cooper et al. 2002). This was a gain of 59%, which is greater than the mean of 24.7% (Table 2) achieved in male rats in 10 lifelong −40% CR studies (Yu et al. 1982; Sprott 1997; Turturro et al. 1999; Thurman et al. 1994; Keenan et al. 1994; Barrows and Kokkonen 1982; Holloszy 1997). Rat survival varies with the strain (Masoro 2002b). The mean gain in 10 female rat CR lifelong studies (Sprott 1997; Turturro et al. 1999; Thurman et al. 1994; Barrows and Kokkonen 1982; Simms and Berg 1962) was also 24.7%. In the CR rat, life extension is largely due to the control of degenerative diseases of the kidney, heart, artery and muscle (Berg and Simms 1965) plus neoplasms and leukemia (Thurman et al. 1994). Prior to the use of specific pathogen-free (SPF) rats, infectious respiratory disease was the major cause of early deaths (Everitt and Cavanagh 1963). Compared with humans, the smaller gain in rat survival is probably due to the use of specific pathogen-free animals (thus eliminating deaths from infectious diseases), and not starting the studies until some considerable time after birth (thus deleting infant and child mortality).

Human life extension in the 20th century in developed countries has been due mainly to reductions in infant and child mortality, the control of infectious diseases and the decline in deaths from cardiovascular disease and cancer since 1970 (Wilmoth 2000). The leading causes of death have shifted from infec-

Table 2. Gains in life expectancy at birth of human populations in 10 developed countries during the 20th century due to improvements in public health and medical care compared with the increased survival of male laboratory rats in 10 long-term 40% calorie restriction studies.

Human life expectancy in years				Mean or median rat survival in days			
Country	1900	2002	%Gain	Rat strain (ref.)	Control	CR	%Gain
Japan	44.5	81.9	84.0	F344 (Yu et al. 1982)	701	986	40.7
Switzerland	50.7	80.6	59.0	BN (Sprott 1997)	903	1,078	19.4
Sweden	55.8	80.4	44.0	BN (Turturro et al. 1999)	935	1,115	19.3
Australia	56.5	80.4	42.3	F344xBN (Turturro et al. 1999)	890	1,180	32.6
France	47.0	79.7	69.6	F344 NIH (Turturro et al. 1999)	760	855	12.5
Italy	44.5	79.7	79.1	F344 PUR (Turturro et al. 1999)	740	910	23.0
New Zealand	59.4	78.9	32.8	F344 (Thurman et al. 1994)	707	875	23.8
Germany	46.6	78.7	68.9	Sprague–Dawley (Keenan et al. 1994)	595	728	22.4
United Kingdom	50.5	78.2	54.9	Sprague–Dawley (Barrows and Kokkonen 1982)	706	924	30.9
USA	49.3	77.3	56.8	Long–Evans (Holloszy 1997)	858	1,051	22.5
Mean	50.5	79.6	59.1	Mean	779.5	970.2	24.7
Standard dev	4.94	1.27	15.7	Standard dev	105.2	130.4	7.59

Data for Human Life Expectancy in 1900 are taken from the United Nations Statistical Yearbook 1955 (United Nations 1957).
Data for Human Life Expectancy in 2002 are taken from the World Health Report 2003 (World Health Organization 2003).
Survival in rodents varies with the strain (Masoro 2002b).
The difference in % gain in survival of humans and rats was significant (t-test, $P < 0.001$).

tious to chronic diseases. It is calculated that elimination of the dozen major causes of death in developed countries would extend the mean life duration by less than 20 years (National Vital Statistics Reports 2004). The numbers of the very old (85 years and more) increased rapidly in the last quarter of the 20th century due to reduced deaths from heart disease, stroke and cigarette-related lung disease and cancer (Broe and Creasey 1995). For similar reasons, there has been a large and continuing increase in the numbers of centenarians (McCormack 2000; Shibata and Haga 1992), which have been doubling every decade since 1960 (Vaupel et al. 1998).

Calorie intake is a modifiable risk factor for vascular disease and mortality. Nonmodifiable risk factors are age, gender, genetic inheritance and race (Slama et al. 2002). In the United States the leading causes of death from modifiable risk factors in the year 2000 (Mokdad et al. 2004) were smoking tobacco (18%), poor diet and physical inactivity (16%) and alcohol (3%). Other causes making up a further 10% were microbial agents, toxic agents, motor vehicle crashes, firearms, sexual behavior and illicit drugs. Approximately half of all deaths can be attributed to modifiable risk factors which lead to premature death (Mokdad et al. 2004; McGinnis and Foege 1993). Overeating and physical inactivity may soon become the leading modifiable cause of death, since cigarette smoking is falling (Kannel and Thom 1984; Sytkowski et al. 1990; Broe and Creasey 1995) and the population is becoming more overweight (Cameron et al. 2003; Must et al. 1999; Fujioka 2002; Peeters et al. 2003; Fontaine et al. 2003).

Calorie restriction mimetics and antiaging therapy/longevity science

The concept of a CR mimetic was introduced by Lane and colleagues (Lane et al. 2002) as an alternative to CR which is very difficult for humans to continue for the long periods of time needed to achieve beneficial effects. A CR mimetic will have the same antiaging effects without the need to reduce food intake. The CR mimetic drugs are able to lower blood pressure and blood cholesterol, important risk factors for the development of cardiovascular disease, in much the same way as CR does in the human and the monkey (Table 1). CR has been shown to inhibit the development of atherosclerosis in the human carotid artery (Fontana et al. 2004). In OECD (Organization for Economic Cooperation and Development) countries, increased pharmaceutical consumption was found to reduce mortality for the population in middle and old age (Miller and Frech 2000). Theoretically a mixture of drugs, nutrients, and other geroprotectors will be required to lower the risk factors for the major killer diseases of later life, the vascular diseases, the cancers, diabetes mellitus,

and dementia, in order to achieve further substantial extension of healthy life in humans. CR can probably do all of this in the rodent and very likely in the monkey and the human. It would be much more convenient if CR mimetics could be used. However, much study will be needed to determine the place of pharmacotherapy in delaying the onset of the diseases of old age. In addition, there are innumerable problems with side effects in multidrug therapy (Routledge et al. 2003; Walker and Wynne 1994; McLean and Le Couteur 2004). CR has a general antiaging effect, whereas the drugs have specific effects, each acting mainly on one disease or pathological process. A number of chemical agents (Masoro 2002c; Bernarducci and Owens 1996; Ingram et al. 2004) may be CR mimetics in experimental animals since they alter the aging rate or extend life, such as 2-deoxyglucose (Lane et al. 2002; Ingram et al. 2004), antioxidants (Bernarducci and Owens 1996) deprenyl (Kitani et al. 2000), melatonin (Anisimov 2003a), carnosine (Hipkiss et al. 2001) coenzyme Q10 (Linnane et al. 2002), dehydroepiandrosterone (DHEA) (Nawata et al. 2002; Percheron et al. 2003), epitalon (Anisimov et al. 2003b), antidiabetic biguanides (Anisimov et al. 2003a) and metformin (Ingram et al. 2004), resveratol (Howitz et al. 2003), and a combination of acetyl-L-carnitine and lipoic acid (Hagen et al. 2002).

Since the secretion of many hormones declines with age, hormone replacement therapy (HRT) has been used to minimize some of the problems of aging (Wathen et al. 2004; Morley 2004). Long-term HRT with estrogen and progestin in perimenopausal women reduces bone loss (Wathen et al. 2004), but increases the risk for breast cancer (Wathen et al. 2004; Tjonneland et al. 2004). However, in aging men HRT with testosterone, DHEA or growth hormone is of doubtful benefit (Janssens 2000; Morley 1999).

Dietary restriction reduces the secretion of most pituitary and target gland hormones (Everitt 2003), including the insulin-like growth factor-1 (IGF-1) (Dunn et al. 1997; Sonntag et al. 1999). Long-term reductions in IGF-1 secretion are associated with increased lifespan (Shimokawa et al. 2003; Carter et al. 2002). Genetic mutant mice with deficiencies of growth hormone and IGF-1, and with reduced IGF-1 signaling, age more slowly and are long lived (Bartke et al. 2001; Longo and Finch 2003; Barbieri et al. 2003; Anisimov 2003b). There is currently a search for the pharmacological modulators of the insulin/IGF-1 signaling pathway which is involved in CR and aging (Longo and Finch 2003; Anisimov 2003b) and probably many cancers (Hursting et al. 2003; Renehan et al. 2004). Longo and Finch (2003) propose three categories of antiaging drugs: (1) to simulate dwarf mutation and therefore decrease growth hormone production by the pituitary, (2) to prevent IGF-1 release from the liver, or (3) to decrease IGF-1 signaling. Anisimov (2003b) suggests that the antidiabetic biguanides could be promising candidates for the prevention of cancer and for lifespan extension.

Since IGF-1 is secreted mainly by the liver, this organ may play a central role in aging particularly in modulating atherosclerosis (Le Couteur et al. 2002a, b), a major determinant of life duration in humans. Aging is a complex interaction between genes and the environment. The liver is a significant point of contact with orally ingested food and xenobiotics. Age-related changes in the liver may partially explain the increased risk of older people to atherosclerosis (Le Couteur et al. 2002a), neurodegenerative diseases (Le Couteur et al. 2002b) and adverse drug reactions (Le Couteur et al. 2005). The liver, and particularly the hepatic sinusoidal endothelium which undergoes age-related changes likely to interfere with substrate transfer (Le Couteur et al. 2005), is a potential target for future CR mimetic agents. More than 50% of the biomarkers of aging in rodents are related to liver pathology (McLean and Le Couteur 2004; Lipman et al. 1999). The liver is a major target of the anticancer effects of CR (Dhahbi et al. 2004). CR rapidly establishes a pattern of hepatic gene expression associated with increased lifespan in rodents (Dhahbi et al. 2004). Thus, therapies which mimic these rapid gene expression biomarkers of CR should prolong life (Dhahbi et al. 2004).

In the absence of a master antiaging drug, the change to a healthy lifestyle of not smoking (Doll et al. 2004; Fraser and Shavlik 2001; Paffenbarger et al. 1993; Ferruci et al. 1999), maintaining a lean body weight (Must et al. 1999; Peeters et al. 2003; Fraser and Shavlik 2001; Paffenbarger et al. 1993; Ferruci et al. 1999) and doing regular physical exercise (Fraser and Shavlik 2001; Paffenbarger et al. 1993; Ferruci et al. 1999) would be expected to increase average and possibly even maximal life expectancy. Thus, a change to a healthy lifestyle in childhood, coupled with a reduced energy intake of a nutritionally rich diet starting soon after maturity

would seem to be the best long-term antiaging strategy. The risk factors for aging diseases should be kept at low levels throughout life with the help of changes in diet and physical activity along with the use of specific drugs.

Conclusion

Human life may be prolonged by using certain drugs or by making changes in lifestyle to delay the onset of life-shortening diseases. Drugs that lower blood pressure and blood cholesterol delay the development of cardiovascular disease and thereby extend human life. CR may act through some common pathways with these drugs, reducing blood pressure and cholesterol in humans, and inhibiting the development of atherosclerosis. Thus, it is most likely that CR will also delay the development of cardiovascular disease and by this means extend average human lifespan. CR has the advantage over drugs of a greater spectrum of activity with the minimum of adverse reactions. For life extension in the future, there is a continuing need to find CR mimetics, drugs, dietary constituents, and lifestyle factors that can lower the risk factors for killer diseases.

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