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Cellular mechanisms of cardioprotection by calorie restriction: state of the science and future perspectives

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Synopsis

Evidence from animal models and preliminary studies in humans indicate that calorie restriction (CR) delays cardiac aging and can prevent cardiovascular disease. These effects are mediated by a wide spectrum of biochemical and cellular adaptations, including redox homeostasis, mitochondrial function, inflammation, apoptosis and autophagy. Despite the beneficial effects of CR, its large-scale implementation is challenged by applicability issues as well as health concerns. However, preclinical studies indicate that specific compounds, such as resveratrol, may mimic many of the effects of CR, thus potentially obviating the need for drastic food intake reductions. Results from ongoing clinical trials will reveal whether the intriguing alternative of CR mimetics represents a safe and effective strategy to promote cardiovascular health and delay cardiac aging in humans.

Keywords

Cardiovascular disease; oxidative stress; inflammation; apoptosis; autophagy; calorie restriction mimetics

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1. Introduction

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in Western countries [1], and it is estimated that by 2020 up to 40% of all deaths will be due to CVD [2]. The impact of CVD is especially pronounced in older populations, where remarkably high prevalence of CVD and incident events are observed, resulting in high levels of disability and mortality [3]. Numerous modifiable risk factors for CVD have been identified, including smoking, hypertension, dyslipidemia, abdominal obesity, impaired insulin sensitivity, and sedentary lifestyle [4]. In addition, advances in the field of cardiovascular biology have unveiled several biomarkers associated with increased CVD risk. Examples include alterations in the redox state favoring a pro-oxidant milieu, enhanced production of inflammatory cytokines, and high levels of pro-inflammatory enzymes, hemostatic factors and adhesion molecules [3,5].

Despite great progress in the diagnosis and management of CVD, the prevalence of heart failure (HF), the final common pathway of many heart diseases, has reached epidemic proportions among older persons [6]. This condition represents a major determinant of chronic disability in the elderly [7]. Furthermore, HF is characterized by extremely poor prognosis, with 1-year mortality rate exceeding 50% in those aged 85 years or older [8]. Hence, there is an urgent need for effective strategies to reduce the incidence and improve the prognosis of CVD, especially in geriatric populations.

Calorie restriction (CR) without malnutrition is to date the most effective intervention for improving health, maintaining function and increasing mean and maximum lifespan in a variety of species [9]. The anti-aging properties of CR reside in the prevention or retardation of several degenerative diseases, including CVD, cancer, neurodegenerative disorders, diabetes and autoimmune diseases [10]. As a result, experimental rodents subjected to lifelong CR display up to 60% maximum lifespan extension compared to ad libitum (AL) fed controls [11]. The magnitude of this effect suggests that dietary restriction affects global and fundamental biological processes underlying aging. In support of this, CR has been shown to delay the onset of age-related cardiac alterations and ameliorate virtually all known CVD risk factors both in experimental animals and humans [12-14]. This protection stems from a multitude of adaptations, such as blood pressure reduction, alterations of the lipoprotein profile, improved glucoregulation, reduction in sympathetic nervous system drive, and hormonal changes [10].

2. Cellular mechanisms of cardioprotection by calorie restriction

At the cellular level, cardioprotection by CR is mediated by various mechanisms, among which attenuation of oxidative stress, mitochondrial dysfunction and inflammation, and a favorable modulation of apoptosis and autophagy are prominent contributors (Table 1). The role that each of these adaptations plays in cardioprotection is discussed in this brief review.

2.1. Oxidative stress and mitochondrial dysfunction

The free radical theory of aging, first proposed by Haman in the 1950s [15] and subsequently refined [16-19], is currently the most widely accepted theory of aging. The main tenet of this theory is that the accumulation of oxidative damage to cellular constituents over the lifespan causes age-related tissue deterioration and ultimately disease conditions. Free radicals and other reactive species are continuously generated by numerous biological processes, with mitochondrial respiration considered the main source. To protect itself against oxidative damage, the cell is equipped with enzymatic [e.g., superoxide dismutase (SOD), glutathione peroxidase (GPx), catalase, thioredoxins] as well as non-enzymatic (e.g., glutathione, vitamin E, vitamin C, β-carotene, uric acid) antioxidant defenses. Redox imbalance, resulting from

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increased oxidant generation and/or reduced antioxidant capacity, causes structural and functional cellular alterations, eventually leading to aging and disease.

Analyses of heart tissues of old rodents [20-25] and humans [26] have shown evidence of elevated levels of oxidative damage to proteins, lipids and DNA. In addition, oxidative stress is involved in the pathogenesis of myocardial ischemia-reperfusion injury [27], cardiac remodeling after myocardial infarction [28], left ventricular hypertrophy (LVH), and HF [29]. Furthermore, oxidative damage plays a central role in endothelial dysfunction both during aging [30] and in the setting of CVD [31].

Studies have shown that CR can prevent or even reverse the cardiovascular accrual of oxidative damage in a variety of experimental settings. Sohal et al. [21] found that cardiac DNA oxidative damage, as determined by 8-hydroxydeoxyguanosine content, was increased in old mice compared to younger controls. Importantly, mice subjected to 40% CR displayed a significant reduction in DNA oxidation relative to AL-fed rodents. Similar findings were reported in rats kept on an alternate-day fasting regimen [23]. In addition, protein carbonyl content (a marker of protein oxidation) increased in the heart of AL-fed rats over the course of aging, which was attenuated by lifelong 40% food intake reduction [20]. Mitigation of protein oxidative damage was sustained by reduced mitochondrial generation of superoxide anion ($O_2^{\bullet -}$) and hydrogen peroxide (H_2O_2) [20]. In addition, catalase activity was reduced during aging in AL-fed mice, whereas an opposite pattern was evident in CR animals. Furthermore, Leeuwenburgh et al. [22] demonstrated that lifelong 40% CR prevented the age-related accumulation of *o*-tyrosine and *o,o′*-dityrosine in the mouse heart. It has also been reported that 12-month 40% CR decreases mitochondrial H_2O_2 generation, free radical leak and oxidative damage to mitochondrial DNA (mtDNA) in the heart of aged rats [32]. A similar dietary regimen also counteracted the age-dependent increase in glycoxidative and lipoxidative damage to rat heart mitochondrial proteins [33]. A later study from the same group demonstrated that even 4-month 40% CR was sufficient to elicit a significant reduction in mitochondrial protein glycoxidation and lipoxidation in the heart of young rats [34]. The efficacy of short-term CR in attenuating heart oxidative stress was further demonstrated by Diniz et al. [35], who reported decreased myocardial levels of lipoperoxidation in young rats subjected to 50% CR for 35 days. In addition, CR rats displayed increased activity of the antioxidant enzymes GPx and catalase relative to AL-fed controls. Finally, 40% CR for 3 months reduced cardiac mitochondrial H_2O_2 generation and protein carbonyl content in middle-aged rats [36].

Although most studies have shown attenuation of cardiac oxidative damage and/or mitochondrial oxidant generation with CR, a few reports did not detect such adaptations [37, 38]. This discrepancy may be ascribed to differences in the dietary regimens employed and/or species-specific differential susceptibility to CR. However, it should also be considered that the heart, similar to skeletal muscle, contains two bioenergetically [39] and structurally [40] distinct mitochondrial subpopulations: subsarcolemmal mitochondria (SSM), located beneath the sarcolemma, and intermyofibrillar mitochondria (IFM), arranged in parallel rows between the myofibrils. Notably, these two populations are differentially affected by aging and display different susceptibility to CR [25]. However, most studies have analyzed either SSM only or a mixed population of SSM and IFM. Our laboratory has recently investigated the effect of lifelong mild CR (i.e., 8% calorie intake reduction), alone or in combination with voluntary wheel running, on mitochondrial H_2O_2 generation and markers of oxidative stress in cardiac SSM and IFM of old rats [41]. CR combined with exercise reduced H_2O_2 generation in both mitochondrial populations. In addition, activity of the mitochondrial SOD isoenzyme (MnSOD) was significantly decreased in SSM and IFM from wheel runners, likely as a result of reduced $O_2^{\bullet -}$ production. However, despite the attenuation of mitochondrial oxidant generation, levels of protein and lipid oxidative damage were not affected by either

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intervention. In another study, Kalani et al. [42], employing an analogous experimental model, found increased plasma total antioxidant capacity in 8% CR rats either sedentary or exercised.

Besides cardiac aging, oxidative stress is also involved in the pathogenesis of several cardiovascular conditions. Mitochondria of the failing heart produce large amounts of reactive oxygen species (ROS) [43]. Moreover, other sources of oxidants (e.g., xanthine oxidase and non-phagocytic NADPH oxidase) can contribute to the development of HF, cardiac remodeling and LVH [44-46]. Furthermore, xanthine oxidase and NADPH oxidase-derived free radicals play a role in the pathogenesis of endothelial dysfunction via scavenging of nitric oxide (NO) by $O_2^{\bullet -}$ [47,48]. Increased ROS generation and oxidative damage are also responsible for cardiac contractile dysfunction following ischemia-reperfusion [27]. Seymour et al. [49] demonstrated that 15% CR reduced cardiac lipid peroxidation in Dahl salt-sensitive rats fed a high-salt diet. Mitigation of oxidative stress ameliorated left ventricular remodeling, improved diastolic function and cardiac index, and delayed the onset of cardiac cachexia. It was also reported that lifelong 40% CR attenuated cardiac oxidative damage in middle-aged rats following myocardial ischemia-reperfusion [50].

Regarding the effects of CR on endothelial function, short-term (i.e., 3 months) 30% food restriction abolished the increases in mitochondrial ROS generation and NADPH-dependent $O_2^{\bullet -}$ production in the coronary endothelium and aortic wall of spontaneously diabetic rats [51]. Furthermore, CR prevented the decrease in total SOD activity in the thoracic aorta. These changes resulted in reduced levels of lipid peroxidation and increased NO availability. Moreover, CR combined with low-intensity physical activity reduced oxidative stress and improved acetylcholine-dependent vasodilation in healthy, middle-aged obese subjects [52].

In summary, although the magnitude of the anti-oxidant effect is influenced by a number of factors, including the degree of dietary restriction, the age when CR is initiated and the duration of the intervention, a wealth of evidence supports a protective effect of CR against oxidative stress in the cardiovascular system.

2.2. Inflammation

Chronic low-grade inflammation is acknowledged as a powerful, independent risk factor for CVD [53]. Moreover, chronic inflammation may be a converging process linking normal aging with age-related diseases [54]. According to this proposition, the age-dependent increase in oxidative stress activates redox-sensitive transcription factors (e.g., NF-κB), which in turn enhance the expression of inflammatory cytokines, cellular adhesion molecules (CAMs) and pro-inflammatory enzymes [54]. Among the inflammatory biomarkers predictive of cardiovascular events, C-reactive protein (CRP), interleukin 6 (IL-6) and tumor necrosis factor-α (TNF-α) have been the most extensively investigated. In addition, myeloperoxidase (MPO) has recently emerged as a novel biomarker of inflammation and oxidative stress in CVD [55]. Of note, it has become clear that these molecules are not mere risk markers, but they indeed play an active role in the pathogenesis of CVD [55-58]. Besides cytokines, CAMs have also been identified as important mediators in the inflammatory process involved in atherosclerosis [59]. Notably, TNF-α and IL-1β are potent inducers of CAM expression [60].

Convincing evidence indicates that CR attenuates the age-related increase in systemic inflammation. Old rodents kept on lifelong 40% CR displayed reduced levels of various inflammatory biomarkers, including TNF-α, IL-6, CRP and several CAMs [42,61-63]. Furthermore, Kalani et al. [42] found that lifelong 8% CR either alone or combined with voluntary wheel running prevented the increase in plasma CRP levels in old rats. In addition, CR attenuated the age-related increase in MPO activity in the rat kidney [64]. Mitigation of systemic inflammation by CR has also been reported in non-human primates [65]. Moreover,

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similar anti-inflammatory effects can be obtained with CR in human subjects [14,66,67], even when dietary restriction is initiated late in life [68].

Regarding the effects of CR on inflammation in the presence of CVD, lifelong 40% food intake reduction attenuated the myocardial inflammatory response to ischemia-reperfusion in rats [50]. Furthermore, 15% CR reduced the plasma levels of IL-6 and TNF-α in salt-sensitive rats fed a high-salt diet [49]. Three-month 30% CR also prevented the increase in transforming growth factor-β_1 (TGF-β_1) levels in the aorta of spontaneously diabetic rats [51].

In summary, available evidence indicates that CR protects against elevation in systemic inflammation. Moreover, this effect may be obtained even with mild restrictions in food intake, which is likely to be more feasible for humans to maintain over the long-term.

2.3. Apoptosis

Apoptosis is a highly conserved and tightly regulated process of programmed cell death, resulting in cellular self-destruction without the induction of inflammation or damage to the surrounding tissue. Apoptosis is essential for numerous biological processes, including embryogenesis and development, cellular turnover, tissue homeostasis, and several immunological functions [69]. However, it is postulated that accelerated elimination of irreplaceable post-mitotic cells, such as cardiomyocytes, may contribute to age-associated loss of function and diseases [70]. Cardiomyocyte removal through apoptosis increases with advancing age [71]. It is hypothesized that enhanced cardiomyocyte apoptosis combined with insufficient replenishment by cardiac stem cells may play a central role in age-related heart remodeling [72,73]. Apart from aging, cardiomyocyte apoptosis occurs as a consequence of ischemia-reperfusion insult [74]. In addition, myocyte loss due to apoptosis is increased in patients with end-stage HF [75]. Elevated levels of cardiomyocyte apoptosis have also been detected in diabetic patients [76], suggesting a role for programmed cell death in diabetic cardiomyopathy. Moreover, apoptosis of smooth muscle cells and macrophages within atherosclerotic plaques contributes to disease progression and plaque instability [77].

Recent evidence indicates that CR mitigates age-related apoptosis in the heart. Analysis of high-density oligonucleotide microarrays revealed that 40% CR started at middle age reduced the expression of pro-apoptotic genes and up-regulated anti-apoptotic transcripts in aged mouse heart [78]. In addition, short-term mild CR may protect the aging myocardium from apoptosis by promoting a splicing shift of the apoptosis regulator Bcl-X, favoring the anti-apoptotic variant Bcl-X_L [79]. A recent study from our laboratory has also shown that lifelong 40% CR counteracts the age-related increase in mitochondrial permeability transition pore (mPTP) opening susceptibility in rat cardiac IFM [80]. Notably, opening of the mPTP is considered an important mechanism for the initiation of mitochondria-mediated apoptosis [81]. Interestingly, 6-month 35% CR reduced the extent of cardiac apoptotic DNA fragmentation in rats subjected to ischemia-reperfusion injury [82]. This effect translated into improved recovery of left ventricular function and limitation of infarct size.

Collectively, these findings indicate that CR attenuates age-associated cardiomyocyte apoptosis. The effectiveness of dietary restriction in mitigating cell death in CVD has not yet been thoroughly investigated. However, given the major role of inflammation [83] and oxidative stress [84] in both age- and disease-related apoptosis, it is conceivable that CR may also counteract cardiomyocyte loss associated with CVD progression.

2.3. Autophagy

Autophagy is an evolutionary conserved process that allows eukaryotic cells to degrade and recycle long-lived proteins and organelles [85]. Besides this housekeeping function, the

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autophagic program is also involved in regulating cell growth and the cellular response to starvation, hypoxia, and invading pathogens [86]. As a cellular quality control mechanism, autophagy is essential for degradation of defective intracellular components, thus preventing the accumulation of cellular "garbage" and its detrimental consequences [19]. Three types of autophagy have been described: macroautophagy, microautophagy, and chaperone-mediated autophagy [87]. Notably, macroautophagy is the only mechanism so far attributed to the degradation of dysfunctional and damaged mitochondria. During macroautophagy (subsequently referred to as autophagy), cells typically sequester portions of cytoplasm, which can include organelles, into double membrane-bound vacuoles (autophagosomes) that are then delivered to lysosomes for degradation [88]. Imperfect autophagy results in altered turnover of cellular constituents, including mitochondria. Furthermore, insufficient digestion of oxidatively damaged macromolecules and organelles leads to the accumulation of undegradable material (e.g., lipofuscin) within the lysosomal compartment [89]. In turn, lipofuscin accumulation may act as a sink for lysosomal enzymes, further impairing the degradation of damaged mitochondria [19].

The importance of autophagy for cardiomyocyte health and survival has been demonstrated in autophagy-deficient animals and cell models. For example, in adult mice, cardiac-specific, temporarily controlled deficiency of Atg5, a protein required for autophagy, led to cardiac hypertrophy, left ventricular dilatation, and contractile dysfunction, accompanied by increased levels of ubiquitination (a process targeting proteins for degradation) [90]. In the same study, Atg7, a protein essential for autophagosome formation, was silenced in rat neonatal cardiomyocytes, resulting in reduction of cell viability as well as morphological and biochemical features of cardiomyocyte hypertrophy [90]. Furthermore, lysosome-associated membrane protein 2 (LAMP2)-deficient mice showed excessive accumulation of autophagic vacuoles and impaired autophagic degradation of long-lived proteins, resulting in cardiomyopathy [91]. Collectively, these findings indicate that constitutive cardiomyocyte autophagy is required for protein quality control and normal cellular structure and function under the basal state.

The role of autophagy in cardiac disease is still controversial. Increased numbers of autophagosomes have been observed in cardiac tissues of patients with cardiovascular disorders such as LVH [92], aortic valve stenosis [93], hibernating myocardium [94], and HF [95]. However, it is unclear whether autophagy contributed to cell death in these conditions or was upregulated in an attempt to prevent it. On the other hand, Yan et al. [96] proposed that in chronically ischemic myocardium, autophagy might function cardioprotectively. This hypothesis was supported by a significant increase in the expression of autophagic proteins and the occurrence of autophagic vacuoles in viable but unlysed cells. In contrast, autophagic markers were down-regulated in the infarcted myocardium. In addition, the autophagic degradation of damaged organelles, misfolded proteins and protein aggregates, and the importance of autophagy in nutrient supply and maintenance of energy homeostasis in times of limitation (e.g., during ischemia) suggest a cardioprotective role.

Preservation of well-functioning autophagy may be particularly important during aging. In fact, the increase in oxidative damage and the concomitant increased frequency of misfolded and damaged proteins, protein aggregates and damaged cell organelles impose a higher demand for functional autophagic cellular quality control at old age. However, it appears that the efficiency of autophagy decreases with age [97-99]. Interestingly, CR has been shown to attenuate the age-related decline of autophagy in the rat liver [100]. While starvation has often been utilized to stimulate autophagy, there are limited data on the effect of lifelong CR on age-related changes in autophagy in the heart. We have recently reported that lifelong 40% CR increased the expression of autophagic markers in the heart from adult and old rats compared to AL controls [101]. Although further research is warranted, it is conceivable that upregulation

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of autophagy by CR may play a cardioprotective role by attenuating oxidative damage accrual during aging and CVD.

4. Evidence for cardioprotection by calorie restriction in humans

Adaptations elicited by long-term CR in human subjects appear to resemble those observed in animal models. Remarkably, inhabitants of Okinawa Island, whose traditional diet contains ~20% and ~40% fewer calories compared to inland Japan and the U.S., respectively, have the longest life expectancy and the greatest percentage of centenarians in the world. The extraordinary longevity and disability-free lifespan of Okinawans result from decreased incidence of conditions such as CVD, stroke and cancer. Although Okinawan centenarians appear to possess a genetic "survival advantage" [102], it is likely that a significant part of their longevity secret resides in their nutrient-rich, low-calorie diet [103].

Apart from this case of naturally occurring CR, accumulating evidence indicates that dietary restriction results in significant improvements in traditional cardiovascular risk factors (e.g., blood pressure, blood glucose, lipids, body composition) among overweight and obese subjects [104-109] as well as in lean individuals [14,66,110]. In contrast, the effect of CR on emerging CVD risk factors (e.g., biomarkers of oxidative stress and inflammation) is less established. However, recent studies suggest that CR may have significant effects on these biological processes as well. Lower levels of CRP, TNF-α, and TGF-β_1 have been detected in middle-aged healthy persons on long-term CR (i.e., 3−15 years) compared to age- and gender-matched healthy controls consuming typical Western diets [14,66]. Interestingly, diastolic heart function, as assessed by Doppler echocardiography, displayed a more youthful pattern in CR individuals relative to controls [14]. Furthermore, in a 6-month randomized controlled trial examining the effect of CR (25% of baseline energy requirements) on biomarkers of longevity and oxidative stress in healthy, non-obese adults, dietary restriction was found to reduce DNA damage in white blood cells (WBC) [111], improve whole body insulin sensitivity [111], enhance skeletal muscle mitochondrial biogenesis [112], and produce favorable changes in systemic inflammation, coagulation, lipid, and blood pressure [113,114]. In a recent study, 12-month CR (20% of baseline energy requirements) improved glucose tolerance and reduced DNA and RNA oxidative damage in WBC of healthy normal and overweight persons aged 50 −60 years [115,116]. Furthermore, Bosutti et al. [67] reported that 20% CR for 2 weeks prevented the increase in circulating levels of CRP and IL-6 in normal weight, healthy men subjected to experimental bed rest. In addition, an 8-day very low calorie diet (600 kcal/day) increased plasma levels of antioxidants and erythrocyte SOD activity, while decreasing levels of lipid peroxidation, in middle-aged obese subjects.

The biological effects of CR in older persons have not yet been thoroughly investigated. However, in a large-scale trial conducted in obese, older adults (≥ 60 years, n = 316), 18-month diet-induced weight loss reduced markers of systemic inflammation (i.e., CRP, IL-6 and soluble TNF-α receptor 1) [68]. Interestingly, weight loss induced by combining diet and exercise did not modify any of the inflammatory biomarkers to a greater extent than diet alone. However, the magnitude of weight loss was lower in the combined program, suggesting that the degree of weight loss or CR may be the key factor contributing to these changes.

In summary, based on studies conducted to date, moderate CR appears to be an effective means for reducing CVD risk in both younger and older persons, including normal weight and overweight individuals. As observed in experimental animals, cardioprotection by CR in humans appears to be mediated by improvement in mitochondrial function and reduction in systemic levels of oxidative stress and inflammation.

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5. Applicability of calorie restriction: calorie restriction mimetics as an alternative strategy

Findings from the obesity literature indicate that most persons are reluctant to engage in long-term CR. In addition, many individuals are unable to sustain CR-induced weight loss, possibly due to internal feedback systems that signal the body to increase food intake or decrease energy expenditure in response to weight loss. Moreover, weight loss may not be advisable in older persons, as it can accelerate age-related muscle loss [118]. Importantly, low body mass index has been associated with increased risk of disability and mortality in older populations [119, 120]. Furthermore, people practicing long-term severe CR may experience several adverse events, including undesired changes in physical appearance, loss of strength and stamina, menstrual irregularities, infertility, loss of libido, osteoporosis, cold sensitivity, slower wound healing, and psychological conditions such as food obsession, depression and irritability [10].

Thus, a critical research question is what degree of CR is tolerable in humans, in order to obtain beneficial physiological changes without incurring adverse events. Animal studies have shown that even mild CR (i.e., 8% calorie intake reduction) may elicit cardioprotective effects [41, 42], thus obviating the need for substantial food intake reductions. If findings from animal studies can be translated to humans, then the amount of CR required for cardioprotection may be more achievable than previously thought. Nevertheless, it will likely be decades before this issue is resolved.

Given the questionable feasibility of long-term dietary restriction, the field of CR mimetics has become a topic of increasing scientific focus. As a general definition, CR mimetics are agents or interventions that are capable of reproducing the effects of CR without requiring food intake reduction [121]. Since the identification of the first agent (2-deoxy-D-glucose) by Lane et al. in 1998 [122], the list of putative CR mimetics has increasingly grown (Table 2). For many of these agents, however, there is little, if any, scientific evidence supporting their efficacy and/or safety.

Among CR mimetics, resveratrol has received the greatest attention. Resveratrol is a naturally occurring polyphenol found in red wine, the notorious cardioprotective effects of which are invoked to explain the so-called “French paradox” [123]. One salient feature of resveratrol resides in its ability to activate sirtuins, which in turn are prominent mediators of lifespan extension by CR [124]. In fact, resveratrol was found to extend the lifespan and delay the onset of aging phenotypes in short-lived organisms by modulating sirtuin signaling [125-127]. With respect to the cardiovascular system, resveratrol has been shown to inhibit cardiomyocyte apoptosis [128], protect the myocardium against ischemia-reperfusion injury [129], prevent LVH [130], improve endothelial function [131], inhibit platelet aggregation [132], and reduce inflammation [133]. In a recent study, resveratrol improved survival and reduced the prevalence of cardiac pathology in mice fed a high-calorie diet [134]. Moreover, resveratrol-supplemented mice displayed better insulin sensitivity and enhanced liver mitochondrial biogenesis compared to animals fed either a standard or high-calorie diet. Of note, short-term supplementation with a nutraceutical mixture containing resveratrol induced a transcriptional shift in murine heart resembling that detected with long-term CR [135]. Lekakis et al. [136] reported that consumption of a red grape polyphenol extract containing resveratrol improved endothelial function in patients with coronary heart disease. Furthermore, 4-week supplementation with a lyophilized grape powder reduced blood lipids, plasma TNF-α and urinary F(2)-isoprostane levels in both pre- and postmenopausal women [137].

In summary, preclinical studies, as well as small clinical trials, appear to support a cardioprotective effect of resveratrol. Results from the numerous ongoing clinical trials testing

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this CR mimetic will likely provide insightful information concerning the efficacy and long-term safety of resveratrol supplementation in human populations.

6. Summary

Despite the indisputable evidence supporting a wide range of beneficial effects of CR, excessive consumption of calorie-dense, nutrient-poor foods, combined with a sedentary lifestyle, has provoked an obesity epidemic in industrialized countries. Adoption of healthier eating habits is feasible by virtually anybody; however, most people are unwilling or unable to engage in substantial food intake restrictions, such as those employed in experimental settings. Furthermore, older persons may be especially prone to experience detrimental effects from dietary restriction if it is excessive or implemented too rapidly. Hence, the optimal level of CR, tailored to specific age groups, is currently unknown and needs to be explored in future studies. Mild CR regimens may provide a valid alternative, as they produce, at least in animal models, significant cardioprotective effects. An intriguing option is represented by CR mimetics, among which resveratrol has emerged as the leading candidate. Results from ongoing clinical trials will reveal whether resveratrol supplementation may provide an effective and safe strategy to improve cardiovascular health in human subjects. Until then, when indulging ourselves with a glass of wine, we can entertain the hope that it does not just warm our heart: it might actually protect it!

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Table 1

CR-induced cellular and molecular changes in aging and CVD.

	Effects of CR	
	Aging	**CVD**
Oxidative stress		
Cardiac DNA damage	↓	---
Heart mitochondrial DNA damage	↓	---
Cardiac protein oxidation	↓	---
Heart mitochondrial protein oxidation	↓	---
Heart mitochondrial oxidant generation	↓	---
Heart antioxidant defenses	↑	↑
Cardiac nitrosative damage	↓	---
Cardiac lipid peroxidation	↓	↓
Endothelium mitochondrial oxidant generation	---	↓
Vascular oxidative damage	↓	↓
Endothelial NO availability	---	↑
Inflammation		
Myocardial TNF-α expression	---	↓
Myocardial IL-1β expression	---	↓
Systemic TNF-α levels	↓	↓
Systemic soluble TNF-α receptor 1 levels	↓	–
Systemic IL-6 levels	↓	↓
Systemic CRP levels	↓	---
Systemic CAM levels	↓	---
Vascular CAM expression	↓	---
Vascular TGF-β_1 levels	---	↓
Apoptosis		
Cardiomyocyte apoptosis	↓	↓
Heart mitochondrial apoptotic signaling	↓	---
Autophagy		
Cardiac autophagy	↑	---
Vascular autophagy	---	---

Abbreviations: CAM, cellular adhesion molecule; CR, calorie restriction; CRP, C-reactive protein; CVD, cardiovascular disease; IL, interleukin; NO, nitric oxide; TGF, transforming growth factor; TNF, tumor necrosis factor.

↑ = increase; ↓ = decrease; --- = not investigated

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Table 2

Candidate CR mimetics listed in alphabetic order. Primary CR mimicking properties of each compound are shown in the right column.

Compound	CR mimicking properties
2-deoxyglucose	Glycolytic inhibitor
4-phenylbutyrate	Antioxidant
Acarbose	Glucose absorption inhibitor
3,5-dimethylpyrazole	Insulin secretion inhibitor, autophagy enhancer
Adiponectin	IGF-1 signaling inhibitor
All-*trans* retinoic acid	IGF-1 signaling inhibitor
Alpha-lipoic acid	Antioxidant
Alpha-phenyl-tert-butyl nitrone	Antinflammatory, antioxidant
Aminoguanidine	Antiglycator
Brain-derived neurotrophic factor	Neuroprotector
Buformin	Gluconeogenesis inhibitor, insulin sensitizer
Butein	Sirtuin activator
Carnitine	Mitochondrial function preserver
Carnosine	Antiglycator
Coenzyme Q10	Antioxidant
Daidzein	IGF-1 signaling inhibitor, glucagon inhibitor
Fenretinide	IGF-1 signaling inhibitor
Fisetin	Sirtuin activator
Genistein	IGF-1 signaling inhibitor
Glyburide	Insulin sensitizer
Gymnemoside	Glucose absorption inhibitor
Iodoacetate	Glycolytic inhibitor
Kaempferol	IGF-1 signaling inhibitor, antioxidant
Metformin	Gluconeogenesis inhibitor, insulin sensitizer
Omega-3 polyunsaturated fatty acids	Antinflammatory
Octreotide	IGF-1 signaling inhibitor
Phlorizin	Urinary glucose excretion promoter
Piceatannol	Sirtuin activator
Pioglitazone	PPAR-γ agonist and insulin sensitizer
Quercetin	IGF-1 signaling inhibitor, antioxidant
Rapamycin	IGF-1 signaling inhibitor
Resveratrol	Sirtuin activator, antinflammatory, antioxidant
Rosiglitazone	PPAR-γ agonist, insulin sensitizer
SC-alpha alpha delta 9	IGF-1 signaling inhibitor
Tamoxifen	IGF-1 signaling inhibitor

IGF-1: insulin-like growth factor-1; PPAR-γ: peroxisome proliferator-activated receptor-γ.