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REVIEW

Therapeutic potential of vitamin D in AGE/RAGE-related cardiovascular diseases

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Abstract

Cardiovascular diseases (CVDs) are among the leading threats to human health. The advanced glycation end product (AGE) and receptor for AGE (RAGE) signaling pathway regulates the pathogenesis of CVDs, through its effects on arterial stiffness, atherosclerosis, mitochondrial dysfunction, oxidative stress, calcium homeostasis, and cytoskeletal function. Targeting the AGE/RAGE pathway is a potential therapeutic strategy for ameliorating CVDs. Vitamin D has several beneficial effects on the cardiovascular system. Experimental findings have shown that vitamin D regulates AGE/RAGE signaling and its downstream effects. This article provides a comprehensive review of the mechanistic insights into AGE/RAGE involvement in CVDs and the modulation of the AGE/RAGE signaling pathways by vitamin D.

Keywords Calcitriol · Diabetic cardiomyopathy · Myocarditis · Ischemia–reperfusion injury · Inflammation

Introduction

A growing body of evidence suggests a pivotal role for advanced glycation end products (AGEs) in the pathogenesis of cardiovascular diseases (CVDs) [1]. Clinical studies have demonstrated that high levels of serum AGEs are associated with an increased incidence of CVDs in individuals both with and without diabetes mellitus (DM) [2, 3]. AGEs represent a class of chemically heterogeneous compounds that are generated when carbonyl groups on reducing sugars or sugar-derived products react with amino groups on proteins, lipids, or nucleic acids and then undergo a series of nonenzymatic reactions. Additionally, the presence of free radicals may oxidize glucose and lipids, resulting in the production of α-oxoaldehydes such as glyoxal, methylglyoxal, and 3-deoxyglucosone, which are precursors of AGEs [4, 5]. AGEs are degraded by lysosomes and eliminated through renal excretion. Hyperglycemia, oxidative stress, inflammation, aging, and renal failure all contribute to the generation of AGEs.

The accumulation of AGEs exerts deleterious effects by altering the structure and function of AGE-modified macromolecules. AGEs interact with the receptor for AGEs (RAGE), a multiligand transmembrane receptor expressed by endothelial cells, inflammatory cells, vascular smooth muscle cells, and cardiomyocytes, leading to an inflammatory and oxidative response [6]. RAGE also interacts with

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high-mobility group box protein 1, advanced oxidation protein products, the S100/calgranulin family, amyloid-β peptide, and other compounds that are released from inflamed, stressed, and damaged cells [7, 8]. Upon ligand binding, RAGE activates multiple cellular signaling pathways, including Janus kinase/signal transducers and activators of transcription (STAT), nicotinamide adenine dinucleotide phosphate hydrogen (NADPH) oxidase, and mitogen-activated protein kinases [9]. These RAGE-mediated signaling pathways lead to the activation of nuclear factor (NF)-κB, with increased production of proinflammatory and proatherogenic mediators and enhanced expression of the RAGE [10, 11]. Therefore, RAGE activation forms a positive feed-forward loop that converts acute inflammatory stimuli into sustained cellular dysfunction, further magnifying tissue damage.

Vitamin D has several critical cardiovascular effects. Vitamin D reduces metabolic disturbances, exerts antioxidant and anti-inflammatory effects, suppresses activity of the renin-angiotensin system, and possesses antihypertrophic and antifibrotic properties in the cardiovascular system [12–14]. Recent studies showed that vitamin D downregulated the expression of RAGE in the heart, suggesting regulatory effects of vitamin D on the AGE/RAGE signaling pathway [13, 15, 16]. This article provides a comprehensive review of the role of AGEs/RAGE in CVDs, and critically analyzes the therapeutic potential of vitamin D for treating CVDs through modulation of AGE/RAGE signaling.

Cellular and molecular evidence supports the role of AGEs/RAGE in CVDs

The progressive accumulation of AGEs impairs the cardiovascular system and manifests as arterial stiffness, atherosclerotic plaque formation, and endothelial dysfunction [4]. In addition, as shown in Fig. 1, activated AGE/RAGE signaling may lead to mitochondrial dysfunction, oxidative stress, calcium dysregulation, and cytoskeletal abnormalities that contribute to the pathophysiology of CVDs.

AGEs' effects on arterial stiffness and atherosclerosis

AGEs cause endothelial dysfunction via suppression of endothelial nitric oxide (NO) generation. Xu et al. demonstrated that the treatment of rabbit aortic rings with AGEs inhibited endothelium-dependent vasorelaxation. AGEs also abolished the NO-dependent vasorelaxant response to shear stress in the rabbit femoral artery [17]. AGEs suppressed endothelial NO synthase (eNOS) activity but did not change eNOS expression in cultured human umbilical vein endothelial cells [17].

AGE-linked collagen is resistant to hydrolytic turnover and accumulates in the vessel matrix in an unorganized and dysfunctional pattern that causes the loss of vascular elasticity [18]. Pharmacological inhibition of AGE cross-links has prevented alterations in myocardial compliance in rats with impaired glucose tolerance [19]. Therefore, AGE-mediated cross-linking plays a crucial role in causing myocardial stiffness and diastolic dysfunction during cardiac remodeling in response to hyperglycemia.

AGE formation in the vascular wall results in cross-linking of collagen molecules to each other and to circulating

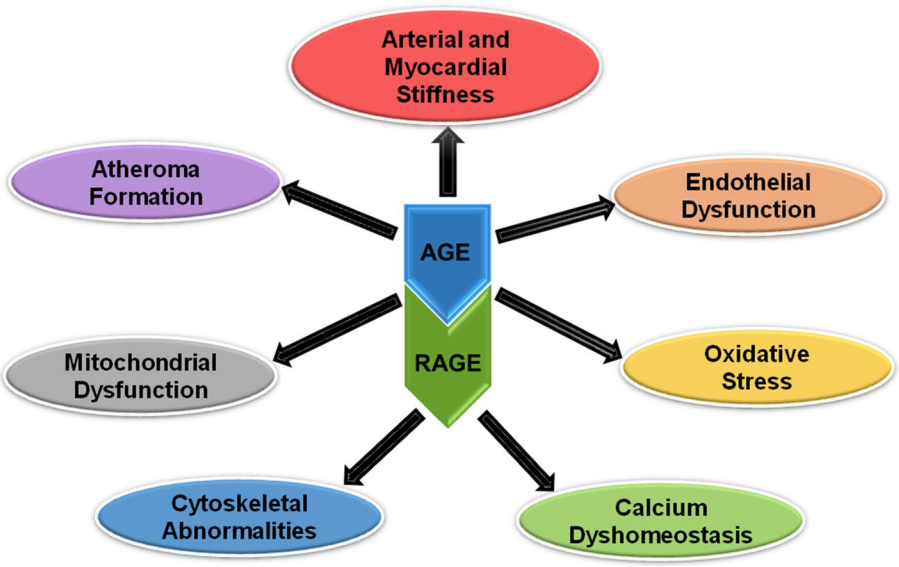

Fig. 1 The role of AGE/RAGE signaling in cardiovascular diseases. AGE/RAGE activation may lead to arterial stiffness, atherosclerosis, endothelial dysfunction, oxidative stress, mitochondrial dysfunction, calcium dysregulation, and cytoskeletal abnormalities that contribute to the pathophysiology of cardiovascular diseases

proteins, which contributes to the genesis of atherosclerotic plaques [18, 20]. Cross-linking between AGE-modified collagen in blood vessel walls and low-density lipoprotein (LDL) significantly impairs the uptake of LDL by its receptor, preventing LDL from being cleared and leading to the development of atheromas [21].

AGEs/RAGE's effects on mitochondrial dysfunction in cardiomyocytes

Mitochondria play a vital role in regulating heart function because the heart is highly dependent on mitochondrial adenosine triphosphate (ATP) production. Disruption of the mitochondrial membrane potential results in altered mitochondrial function and impaired ATP synthesis [22]. In one study, cardiomyocytes treated with AGEs displayed contractile dysfunction that was associated with mitochondrial membrane potential depolarization, which supports the premise that mitochondrial dysfunction has a role in AGE-induced cardiomyocyte dysfunction [23]. Ceramides, a family of waxy lipid molecules, are associated with mitochondrial dysfunction and CVDs [24]. Rat cardiomyocytes (H9C2 cells) treated with AGEs had significantly decreased mitochondrial respiration in a ceramide-dependent manner. Exposure to secondhand cigarette smoke led to reduced mitochondrial respiration and increased ceramide accumulation in the left ventricle of wild-type mice but not in RAGE-knockout mice, suggesting RAGE–ceramide axis has a role in mediating AGE-induced mitochondrial dysfunction in cardiomyocytes [25].

AGEs/RAGE's effects on oxidative stress

RAGE signaling is involved in the pathogenesis of vascular complications in DM through the generation of oxidative stress. AGEs bind to RAGE, thereby inducing reactive oxygen species (ROS) production through the activation of NADPH oxidase and NF-κB signaling. Furthermore, elevated cytosolic ROS levels following RAGE activation facilitates mitochondrial ROS overproduction [26]. The increased ROS and NO levels following AGE–RAGE interaction lead to *S*-nitrosylation of calcium regulatory proteins, which disturbs calcium homeostasis in cardiomyocytes [27]. AGEs also enhance expression of vascular cell adhesion molecule-1, a protein that contributes to atherosclerosis, in cultured human endothelial cells through RAGE-induced oxidative stress [28].

AGEs/RAGE's effects on calcium homeostasis

Calcium is a vital regulator of excitation–contraction coupling in cardiomyocytes. Altered myocardial calcium homeostasis plays a major role in the pathophysiology of heart failure [29, 30]. AGEs reduce the intracellular calcium transient amplitude in a dose-dependent manner and decrease the sarcoplasmic reticular (SR) calcium content without changing the expression of calcium transport proteins in neonatal rat cardiomyocytes [27]. Cardiomyocytes from transgenic mice that overexpressed RAGE exhibited reductions in both systolic and diastolic intracellular calcium concentrations [31]. The increase in calcium transient decay time was shown to be a characteristic feature of diabetic cardiomyopathy [32]. Exposure to AGEs significantly prolonged the decay time of calcium transients in cardiomyocytes from control mice, with an augmentation in this response found in cardiomyocytes from RAGE-overexpressed transgenic mice. Neither AGE treatment nor RAGE overexpression had an effect on protein expression of major calcium regulatory transporters, including sarcoendoplasmic reticular Ca^{2+}-ATPase isoform 2, Na^{+}/Ca^{2+} exchanger 1, and phospholamban in cardiomyocytes [31]. Ryanodine receptor type 2 (RyR2) is the principal transporter that mediates calcium release from the SR in cardiomyocytes. A dysfunctional RyR2 contributes to the pathogenesis of heart failure. AGEs increase the activity of RyR2 through enhancing oxidative stress in neonatal rat ventricular myocytes. Hyperactive RyR2-induced SR leakage depleted Ca^{2+} contents in the SR, resulting in a decrease in systolic Ca^{2+} transients and consequent contractile dysfunction. Blocking RAGE with anti-RAGE immunoglobulin G completely restored the reductions in SR Ca^{2+} contents and systolic Ca^{2+} transients caused by AGE stimulation [33]. Additionally, the RAGE and β1-adrenergic receptor physically interact with each other and form a protein complex that activates Ca^{2+}/calmodulin-dependent kinase II signaling, leading to cardiomyocyte death and myocardial remodeling in response to myocardial infarction, pressure overload, or DM [34].

AGEs/RAGE's effects on cytoskeletal abnormalities

Stabilization of microtubules has been implicated in the development of diabetic cardiomyopathy. AGEs promote microtubule stabilization through RAGE-dependent suppression of the sirtuin 2/acetylated α-tubulin signaling pathway, contributing to left ventricular systolic dysfunction in rats with streptozotocin-induced DM [35]. Moreover, rats developed cardiac hypertrophy, fibrosis, and systolic dysfunction following 8 weeks of treatment with glycated bovine serum albumin (50 mg/kg/day). The expression of profilin-1, an actin-binding protein implicated in cardiac remodeling, was markedly increased in cardiac tissue of AGE-treated rats. Knockdown of profilin-1 ameliorated the myocardial damage caused by AGEs [36].

Therapeutic agents targeting AGEs for the treatment of CVDs

Several agents with inhibitory effects on AGE formation have shown promising outcomes for treating CVDs [37]. Table 1 summarizes the published studies that have addressed therapeutic agents targeting AGEs for the treatment of CVDs. Administration of aminoguanidine, an inhibitor of AGE formation, to rats prevented age-related arterial stiffness and cardiac hypertrophy without altering the collagen or elastin contents of arterial walls, suggesting that aminoguanidine is associated with a reduction in the cross-linking of AGEs and the extracellular matrix [38, 39]. Aminoguanidine also reduced aortic atherosclerotic plaque formation by 30–49%, and the effect was independent of its hypolipidemic or antioxidant potentials in nondiabetic rabbits that were fed a high-cholesterol diet [40]. Treatment with aminoguanidine decreased circulating low-density lipoprotein (LDL) levels by 28% in patients with DM [41]. However, clinical use of aminoguanidine is limited by safety concerns such as the development of gastrointestinal symptoms and hepatic and renal abnormalities [18, 42]. Benfotiamine, another inhibitor of AGE formation, rescued cardiomyocyte contractile dysfunction without affecting hyperglycemia in mice with streptozotocin-induced diabetes [43].

Alagebrium, which can selectively cleave abnormal AGE-protein cross-links, improved endothelial function in patients with isolated systolic hypertension [44]. This improvement was correlated with a reduction in circulatory biomarkers of vascular remodeling, inflammation, and fibrosis. Alagebrium significantly attenuated large artery stiffness and myocardial structural changes in experimental diabetes [45, 46]. Alagebrium also significantly increased the compliance of the left ventricular chamber as well as aortic and carotid arteries in old normotensive nondiabetic primates, thus optimizing coupling between the heart and vasculature [47]. A clinical trial in aged humans with vascular stiffening showed that alagebrium was well tolerated and improved total arterial compliance [48]. Treatment with alagebrium for 16 weeks in elderly patients with diastolic heart failure reduced the left ventricular mass and improved left ventricular diastolic filling [49]. However, a prospective randomized control trial that enrolled patients with systolic heart failure revealed that treatment with alagebrium for 36 weeks did not improve exercise tolerance and had no effects on systolic or diastolic heart function [50].

Clinical and translational evidence of the RAGE in the pathogenesis of CVDs

RAGE signaling has been implicated in the pathogenesis of several cardiac injuries (Table 2). Both alagebrium treatment and RAGE-knockout reduced inflammation, oxidative stress, and mitochondrial dysfunction in cardiac tissue of mice that were fed a Western-style high-fat diet [51]. Mice with streptozotocin-induced diabetes had markedly decreased left ventricular contractility, which was protected by RAGE gene knockdown [23]. Blockage of RAGE signaling with a RAGE antibody prevented the development of increased left ventricular diastolic chamber stiffness and systolic dysfunction in db/db mice, a widely used animal model of type 2 DM [52]. Moreover, peroxisome proliferator-activated receptor-γ agonist treatment suppressed myocardial RAGE and connective tissue growth factor expression, attenuated cardiac fibrosis, and ameliorated diastolic dysfunction in rats with type 2 DM [53].

Table 1 Therapeutic agents targeting advanced glycation end products (AGEs) for the treatment of cardiovascular diseases

Study subject	Intervention	Main findings
Aged rats	Aminoguanidine	Prevented age-related arterial stiffening and cardiac hypertrophy [38, 39]
Rabbits fed a high-cholesterol diet	Aminoguanidine	Reduced aortic atherosclerotic plaque formation [40]
Mice with streptozotocin-induced diabetes	Benfotiamine	Improved cardiomyocyte contractile dysfunction [43]
Rats with streptozotocin-induced diabetes	Alagebrium	Reversed diabetes-induced large artery stiffness and myocardial structural changes [45, 46]
Older nondiabetic monkeys	Alagebrium	Increased compliance of the LV and aortic and carotid arteries [47]
Patients with type 2 DM and end-stage renal disease	Aminoguanidine	Decreased circulating LDL cholesterol levels [41]
Patients with isolated systolic hypertension	Alagebrium	Improved endothelial function of the brachial artery [44]
Aged humans	Alagebrium	Improved arterial compliance [48]
Patients with diastolic heart failure	Alagebrium	Decreased the LV mass and improved LV diastolic filling and quality of life [49]
Patients with systolic heart failure	Alagebrium	Did not improve exercise tolerance or cardiac function [50]

DM diabetes mellitus, *LDL* low-density lipoprotein, *LV* left ventricle

Table 2 Translational evidence of receptor for advanced glycation end products (RAGE) in the pathogenesis of cardiovascular diseases

Study subjects	Intervention	Main findings
Mice fed a high-fat diet	RAGE knockout	Reduced cardiac inflammation, oxidative stress, and mitochondrial dysfunction [51]
Mice with streptozotocin-induced diabetes	RAGE knockdown	Recovered the decrease in LV contractility caused by DM [23]
db/db diabetic mice	Anti-RAGE antibody	Prevented the development of increased LV chamber stiffness and systolic dysfunction [52]
Cardiac troponin I-induced experimental autoimmune myocarditis in mice	RAGE knockout	Suppressed inflammation in the heart [54]
Porcine cardiac myosin-induced experimental autoimmune myocarditis in rats	Soluble RAGE treatment during the early antigen-priming phase	Attenuated experimental autoimmune myocarditis development and improved cardiac function [55]
Myocardial ischemia–reperfusion injury in mice	Homozygous RAGE-null mice	Decreased the infarct size, reduced cardiomyocyte death, and improved functional recovery [56, 57]
Myocardial ischemia–reperfusion injury in rats	RAGE knockdown	Restored electrophysiological abnormalities and abolished ventricular arrhythmias [58]
Myocardial ischemia–reperfusion injury in mice	Molecular imaging to quantify myocardial RAGE expression	Upregulation of RAGE expression, which was mainly colocalized with injured cardiomyocytes undergoing apoptosis [59]

DM diabetes mellitus, *LV* left ventricle

RAGE knockout attenuated cardiac dysfunction in mice with experimental heart failure caused by immune responses to the administration of cardiac troponin I [54]. Similarly, rats with porcine cardiac myosin-induced experimental autoimmune myocarditis had increased cardiac expression of the RAGE, and blocking RAGE activation during the early antigen-priming phase suppressed acute and chronic inflammation, leading to improved cardiac function. However, blocking the RAGE at a later stage did not attenuate the development of experimental autoimmune myocarditis in rats, suggesting that RAGE-mediated inflammation might be critical for the initiation of myocarditis [55]. Taken together, RAGE may play a vital role in the pathogenesis of inflammatory heart disease.

Growing evidence supports a crucial role for RAGE in the pathophysiology of cardiac ischemia–reperfusion injury. RAGE expression was significantly enhanced in the ischemic-reperfused myocardium of rats. Homozygous RAGE-null mice exhibited smaller infarct sizes, reduced contractile impairment, and decreased apoptosis following myocardial ischemia–reperfusion injury [56, 57]. RAGE modulated the cardiac response to ischemia–reperfusion injury through STAT and c-Jun N-terminal kinase signaling [57]. Reduced expression of connexin 43, a major ventricular gap junction protein, increased the incidence of ventricular arrhythmias caused by coronary artery occlusion in mice. RAGE downregulation may lead to antiarrhythmic effects by inducing connexin 43 expression through the activation of the Wnt/β-catenin pathway. Therefore, modulating RAGE might have cardioprotective effects on postinfarct ventricular arrhythmias [58]. Novel molecular imaging by single-photon emission computed tomography showed early upregulation of RAGE expression after myocardial injury, with RAGE mainly colocalizing with injured cardiomyocytes undergoing apoptosis [59]. These findings imply that targeting RAGE is a promising therapeutic strategy for myocardial ischemia–reperfusion injury.

The role of the soluble RAGE in CVDs

The structure of the membrane-bound full-length RAGE can be divided into three parts: an extracellular domain, a transmembrane domain, and an intracellular cytoplasmic tail. The extracellular domain of RAGE is responsible for ligand binding, and the intracellular cytoplasmic tail is essential for transducing RAGE-mediated signaling [6, 10, 11, 60]. In addition to the membrane-bound full-length RAGE, soluble RAGE (sRAGE), which is the truncated isoform of the RAGE, has also been identified in circulation. The role of sRAGE in biological systems is not yet completely understood. Because sRAGE comprises only the extracellular domain of the full-length RAGE, the lack of downstream signaling activation upon ligand-sRAGE binding suggests that sRAGE may be an AGE decoy receptor and might act as an endogenous competitive inhibitor of RAGE. sRAGE is generated by either alternative splicing of RAGE premessenger ribonucleic acid (pre-mRNA) transcripts or proteolytic cleavage of the extracellular domain at the cell surface [6, 60, 61].

Administration of sRAGE not only suppressed the development of atherosclerosis but also stabilized established

atherosclerosis in diabetic apolipoprotein E-null mice [62, 63]. Treatment with sRAGE or RAGE knockdown reduced both the infarct size and fibrosis in rat myocardium with ischemic–reperfusion injury. Combined treatment using both strategies exhibited synergistic cardioprotective effects [64]. Pretreatment with sRAGE diminished apoptosis and inhibited mitochondrial membrane potential depolarization, mitochondrial permeability transition pore opening, and mitochondrial cytochrome C leakage caused by hypoxia-reoxygenation damage in neonatal rat ventricular myocytes [65]. Therefore, the protective effect of sRAGE on cardiac ischemic–reperfusion injury involves its anti-apoptotic potential that is achieved through the modulation of mitochondrial function in cardiomyocytes. Accordingly, the circulating sRAGE levels are thought to be inversely correlated with serum AGE concentrations. Plasma sRAGE concentrations were significantly lower in patients with DM than in nondiabetic controls and were inversely associated with the carotid intima-media thickness [66]. A significant inverse relationship between circulating sRAGE levels and left ventricular hypertrophy in patients with chronic kidney disease (CKD) has been found [67]. Conversely, it has been shown that serum sRAGE levels were positively associated with circulating AGEs in the general population without apparent DM, CVDs, or renal disease [68]. Patients with acute coronary syndrome also had higher serum sRAGE levels than a control group [69]. Thus, circulating sRAGE concentrations may represent a balance between the protective response and RAGE expression in tissue in distinct disease states.

Vitamin D metabolism

Vitamin D is a group of fat soluble molecules involved mainly in the maintenance of calcium and phosphorus homeostasis. There are six known forms of vitamin D referred to as vitamin D_2 through vitamin D_7. Most of the differences between these forms relate to the structure of their side chains [70, 71]. Vitamin D_2 and D_3 exhibit significantly higher biological activity among the six forms (D_2–D_7) of vitamin D [72]. The characteristics of D_4, D_5, D_6, and D_7 have been addressed in the literature and are beyond the scope of this review [72, 73]. Humans receive vitamin D through sunlight exposure and dietary intake of foods such as fatty fish, egg yolks, mushrooms, and dietary supplements. Most of the vitamin D that is consumed in food and supplements are in the form of vitamin D_2 (ergocalciferol) and D_3 (cholecalciferol). Vitamin D_2 is produced from solar UV-B irradiation of ergosterol, which is a steroid found in plants and fungi. Vitamin D_3 is synthesized through UV-B irradiation of 7-dehydrocholesterol in the skin. The most abundant form of vitamin D in animals is vitamin D_3 [70, 72]. Both vitamin D_2 and D_3 are metabolized in the liver to 25-hydroxyvitamin D (25(OH)D), an established indicator of a person's vitamin D status [74]. 25(OH)D requires hydroxylation in the kidneys to form 1,25-dihydroxyvitamin D (calcitriol) to exert its biological activity as a modulator of gene expression [12, 13]. Vitamin D_3 appears to be more efficacious at raising serum 25(OH)D levels than vitamin D_2, suggesting that vitamin D_3 might be the preferred choice for supplementation [75].

Biological effects of vitamin D on cardiovascular health

Vitamin D deficiency has been associated with CVDs based primarily on the results of observational studies. Vitamin D deficiency is most commonly caused by inadequate sun exposure [76, 77]. Several investigations in America and Europe have indicated an inverse correlation between serum 25(OH)D levels and geographical latitude, likely due to reduced skin exposure to sunlight [78]. The British Regional Heart Study, which involved 7735 middle-aged men followed for 6.5 years, demonstrated a twofold higher risk of ischemic heart disease in men from Scotland compared with those from the south of England [79]. Similarly, multiple analyses from other European countries have revealed an increase in ischemic heart disease mortality rates associated with an increase in geographic latitude [78]. Vitamin D deficiency is widely observed in patients with CKD [80]. Serum 25(OH)D levels started to decrease as the estimated glomerular filtration rate decreased to less than 60 mL/min/1.73 m^2 in a Korean adult population [81]. A meta-analysis of 6853 patients with CKD found that an increase of 10 ng/mL in serum 25(OH)D concentrations led to a significant decrease of 14% in mortality risk [82]. These findings suggest that vitamin D deficiency may contribute to the development of CVDs.

Vitamin D and cardiovascular mortality

A prospective observational study involving 247,574 participants from the general population indicated a reverse J-shaped relationship between serum 25(OH)D concentrations and cardiovascular mortality, with the lowest mortality rate at 28 ng/mL [83]. A dose–response meta-analysis of 180,667 individuals revealed that cardiovascular mortality decreased by 12% with an increase of 10 ng/mL in serum 25(OH)D levels [84]. By contrast, a large randomized controlled trial, the Vitamin D and Omega-3 Trial (VITAL), that studied 25,871 healthy participants demonstrated that daily supplementation with 2000 IU of vitamin D_3 did not result in a lower incidence of cardiovascular mortality compared with placebo over a median follow-up period of 5.3 years [85]. The failure of vitamin D supplementation to

reduce cardiovascular mortality in this trial was thought to be caused in part by relatively high baseline serum 25(OH) D levels (30.8 ng/mL) in participants and an insufficient follow-up duration.

Vitamin D and hypertension

A prospective 2-year follow-up study including 2456 participants found that the baseline serum levels of 25(OH)D were not associated with the risk of incident hypertension [86]. A meta-analysis of 283,537 individuals found that the risk of developing hypertension decreased by 12% for every 10 ng/mL increase in baseline serum 25(OH)D concentration [87]. Another meta-analysis involving 142,255 individuals showed that a 10% increase in levels of 25(OH)D caused a significant decrease in systolic blood pressure of 0.37 mmHg as well as a decrease in diastolic blood pressure of 0.29 mmHg [88]. A randomized placebo-controlled trial indicated that taking daily 3000 IU of vitamin D_3 supplementation for 20 weeks resulted in a significant reduction in 24-h blood pressure only among individuals with baseline 25(OH)D levels that were less than 32 ng/mL [89]. However, a meta-analysis that included 46 randomized placebo-controlled trials with a total of 4541 participants found that vitamin D supplementation may be ineffective for lowering blood pressure [90]. The negative conclusion of this meta-analysis was speculated to be attributable to the high variations in administered dose, intervention duration, and study population characteristics, all of which might have affected the outcome of vitamin D supplementation on blood pressure [91].

Vitamin D and coronary artery disease

Clinical evidence suggests an inverse relationship between serum vitamin D levels and the risk of coronary artery disease. A prospective observational study involving 6436 participants without any known CVDs at baseline showed that lower serum 25(OH)D concentrations were associated with an increased risk of incident coronary artery disease over a median follow-up period of 8.5 years [92]. Low levels of vitamin D also predicted the occurrence of coronary artery disease in patients with hypertension [93]. However, vitamin D might not reduce the risk of myocardial infarction, since the VITAL study found that daily supplementation with 2000 IU of vitamin D_3 for 5 years did not reduce the incidence of myocardial infarction among healthy adults [85]. A meta-analysis of 21 studies that included 13,033 individuals demonstrated that vitamin D supplementation did not reduce the risk of coronary artery disease [94]. The discrepancy in dosage regimen of vitamin D supplementation and highly variable comorbidities in the studied patients may lead to controversy regarding the effects of vitamin D on the prevention of coronary artery disease.

Vitamin D and stroke

Men with serum 25(OH)D levels lower than 20 ng/mL had a 1.7-fold higher risk of having a stroke compared with those with 25(OH)D levels greater than 20 ng/mL during a follow-up period of 5.9 years [95]. An analysis of 387 patients who were hospitalized for ischemic stroke revealed a significant negative correlation between serum 25(OH)D levels and the volume of brain infarct measured using magnetic resonance imaging [96]. The stroke patients with lower vitamin D levels had a higher risk of stroke recurrence during 24 months of follow-up [97]. The VITAL study showed that supplementation with vitamin D_3 did not protect against stroke in 25,871 healthy participants [85].

Vitamin D and heart failure

Compared with subjects with serum 25(OH)D levels greater than 30 ng/mL, the hazard ratio for developing heart failure was 1.31 for subjects whose 25(OH)D levels were between 16 and 30 ng/mL and 2.01 for subjects with 25(OH)D levels lower than 15 ng/mL among 27,686 participants aged over 50 years who were subject to follow-up for an average of 1.3 years [98]. A prospective study comprising 6459 participants without clinical CVDs at baseline from racially and ethnically diverse populations demonstrated that an association between 25(OH)D and risk of incident heart failure did not exist over a mean follow-up duration of 8.5 years [99]. Interventional studies investigating the therapeutic effect of vitamin D on heart failure also yielded inconsistent results. One year of vitamin D_3 (4000 IU daily) supplement resulted in a reversal of left ventricular dilatation and a significant improvement in ejection fraction in patients with systolic heart failure and serum 25(OH)D levels lower than 20 ng/mL [100]. Treatment with a daily dose of 4000 IU of vitamin D_3 in patients with heart failure and serum 25(OH)D levels lower than 30 ng/mL for 3 years did not reduce mortality [101]. The relatively high risk of hypercalcemia in patients receiving vitamin D suggests that the dosage of vitamin D used in this trial may not have been optimal. A meta-analysis of seven randomized controlled trials that evaluated the effects of vitamin D on cardiovascular outcomes in patients with heart failure revealed that vitamin D supplementation decreased serum levels of tumor necrosis factor-α, C-reactive protein, and parathyroid hormone, although left ventricular function and exercise tolerance were not changed after intervention [102].

Vitamin D modulates AGE/RAGE signaling and affects CVDs

A growing body of evidence indicates that vitamin D affects AGE/RAGE signaling. Calcitriol attenuates human glycated albumin-induced interleukin (IL)-6 and IL-8 production in gingival fibroblasts [103]. Human glycated albumin alters the expression of genes involved in steroid production and affects folliculogenesis in human luteinized granulosa cells. Calcitriol diminishes the effects of human glycated albumin on granulosa cells, possibly by downregulating RAGE expression [104, 105].

The link between vitamin D and cardiovascular AGE/RAGE signaling

Multiple laboratory findings suggest the association between vitamin D and cardiovascular AGE/RAGE signaling (Table 3). An in vitro study demonstrated that both vitamin D_3 and calcitriol prevented glycation modification in human serum albumin induced by the incubation of glucose (20 mM) [106]. Vitamin D_3 supplementation for 10 weeks reduced AGE accumulation in the aortic wall of rats with streptozotocin-induced diabetes [107]. Calcitriol diminished the upregulation of RAGE expression, IL-6 levels, and NF-κB activity in human umbilical vein cord endothelial cells stimulated with AGEs [108]. Our previous study demonstrated that calcitriol attenuated RAGE expression in the hearts of rats with streptozotocin-induced diabetes, which might have been caused by the suppressive effects of calcitriol on the renin–angiotensin system and its anti-inflammatory and antioxidative actions [15]. A microRNA microarray analysis revealed that calcitriol had beneficial effects on the expression profile of microRNAs and their target genes in endothelial cells incubated in a medium containing high glucose concentrations and AGEs to mimic DM [109].

Mechanisms underlying the effect of vitamin D on AGE/RAGE signaling

Vitamin D alleviates oxidative stress and inflammatory response, both of which are the preferred environments for AGE/RAGE activation. Vitamin D might suppress RAGE expression through its inhibitory effect on NF-κB activity [110]. Calcitriol downregulated RAGE expression through a disintegrin and metalloprotease 10 (ADAM10)-mediated proteolytic cleavage of RAGE in HL-1 cardiomyocytes. In addition, calcitriol activated ADAM10 and stimulated RAGE pre-mRNA alternative splicing, leading to increased generation of sRAGE in cardiomyocytes [16]. These findings suggest that calcitriol has therapeutic potential for treating RAGE-mediated cardiovascular complications (Fig. 2).

Clinical findings of vitamin D's effect on AGE/RAGE signaling

Clinical investigations of the relationship between serum vitamin D levels and the AGE load have shown contradictory findings (Table 4). Cross-sectional studies revealed no significant association between serum vitamin D levels and skin autofluorescence, a marker of skin AGE accumulation suggestive of the long-term AGE cumulative burden, in apparently healthy subjects [110] or patients with DM [111]. By contrast, a prospective cohort study of the general population demonstrated that serum 25(OH)D concentration measured at baseline was inversely correlated with skin autofluorescence assessed 11.5 years later [112]. Krul-Poel et al. also found that serum vitamin D status was inversely associated with skin autofluorescence in patients with well-controlled type 2 DM. Although a 6 month period of vitamin D supplementation (50,000 IU monthly) had no effect on the level of skin AGE accumulation in subjects with a mild vitamin D deficiency (24 ng/mL) at baseline [113], a randomized controlled trial showed a significant reduction in skin autofluorescence in patients with nondiabetic CKD and a marked vitamin D deficiency (< 16 ng/mL) who received oral vitamin D_2 (50,000 IU weekly for 1 month followed by 50,000 IU monthly) for 6 months [114].

Table 3 Link between vitamin D and cardiovascular advanced glycation end product (AGE)/receptor for AGEs (RAGE) signaling

Treatment effects	Main findings
Vitamin D_3 and calcitriol on human serum albumin	Prevented glycation modification in human serum albumin induced by the incubation of glucose (20 mM) [106]
Vitamin D_3 in rats with streptozotocin-induced DM	Reduced AGE accumulation in the aortic wall [107]
Calcitriol on human umbilical vein cord endothelial cells treated with AGEs and high glucose concentrations	Diminished RAGE upregulation [108] Beneficial effects on microRNAs and their target gene expressions [109]
Calcitriol on mouse cardiomyocytes	Directly downregulated RAGE expression [16]
Calcitriol in rats with streptozotocin-induced DM	Attenuated RAGE upregulation in diabetic hearts [15]

DM diabetes mellitus

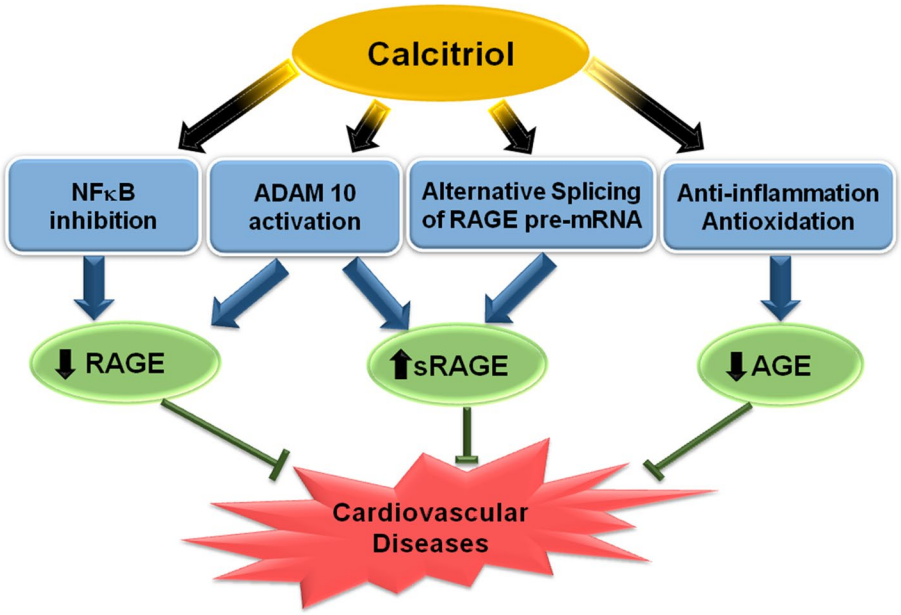

Fig. 2 Schematic illustration of the proposed mechanisms underlying the effects of vitamin D on AGE/RAGE signaling. Vitamin D inhibits AGE formation, suppresses RAGE expression, and stimulates sRAGE production through multiple mechanisms. ADAM10, a disintegrin and metalloprotease 10; NF-κB, nuclear factor-κB; sRAGE, soluble RAGE

Table 4 Clinical effects of vitamin D on advanced glycation end products (AGE)/receptor for AGEs (RAGE) signaling

Study population	Intervention	Main outcomes
119 healthy people and 27 patients with hypertension	None	No association between serum vitamin D levels and skin AGE accumulation [110]
43 patients with type 1 DM, 233 patients with type 2 DM, 121 nondiabetic controls	None	No association between serum vitamin D levels and skin AGE accumulation [111]
245 patients with type 2 DM	None	The serum vitamin D status was inversely associated with skin AGE accumulation [113]
245 patients with type 2 DM	Vitamin D, 50,000 IU/month for 6 months	No effect on the accumulation of skin AGEs [113]
38 patients with nondiabetic stage 3 or 4 chronic kidney disease	Vitamin D_2, 50,000 IU weekly for 1 month followed by 50,000 IU monthly for 6 months	Significant reductions in skin AGE accumulation [114]
67 women with polycystic ovary syndrome	Vitamin D_3, 50,000 IU once weekly for 8 weeks	Significantly increased serum sRAGE levels [115]
51 hemodialysis patients	Calcitriol, 2 μg twice weekly for 8 weeks	Significantly increased serum sRAGE levels [116]
88 patients with stage 3 or 4 chronic kidney disease	Paricalcitol, 2 μg once daily for 12 weeks	Did not change serum levels of AGEs or the sRAGE [117]

DM diabetes mellitus, *sRAGE* soluble RAGE

Few clinical studies have addressed the effects of vitamin D on serum sRAGE levels. Administration of vitamin D_3 (50,000 IU once weekly) for 8 weeks in women with polycystic ovary syndrome and a vitamin D deficiency led to a rise in circulating sRAGE levels. The increase in the serum sRAGE was positively associated with the increase in serum vitamin D levels [115]. Calcitriol treatment for 8 weeks significantly increased serum concentrations of sRAGE in hemodialysis patients [116]. By contrast, paricalcitol, a synthetic vitamin D receptor activator, did not change serum levels of AGEs or the sRAGE in patients with CKD [117]. Therefore, an individual's serum vitamin D status and the dosage of vitamin D replacement might affect outcomes of vitamin D treatment on AGE/RAGE modulation. It will be useful to perform large-scale randomized controlled trials of vitamin D treatment to evaluate the regulatory effects of vitamin D on AGE/RAGE signaling to clarify the treatment potential of vitamin D.

Conclusions

Substantial evidence implies a crucial role of AGE/RAGE signaling in cardiovascular health. AGE accumulation leads to blood vessel and myocardial stiffness, atherosclerotic plaque formation, and endothelial dysfunction. RAGE

activation results in aggravated oxidative stress, mitochondrial dysfunction, disturbed calcium homeostasis, aberrant cytoskeletal dynamics, increased cardiomyocyte apoptosis, and contractile impairment. Regulating the AGE/RAGE pathway holds promise for treating cardiac ischemic–reperfusion injury, diabetic cardiomyopathy, and inflammatory heart diseases. Experimental findings have shown that vitamin D suppresses AGE accumulation, downregulates RAGE expression, and enhances sRAGE production, implying that vitamin D may be a potential therapeutic strategy for treating CVDs.

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