Vitamin D and advanced glycation end products and their receptors

Sorayya Kheirouri, Mohammad Alizadeh

PII: S1043-6618(20)31187-7

DOI: https://doi.org/10.1016/j.phrs.2020.104879

Reference: YPHRS 104879

To appear in: *Pharmacological Research*

Received Date: 27 March 2020

Accepted Date: 27 April 2020

Please cite this article as: Kheirouri S, Alizadeh M, Vitamin D and advanced glycation end products and their receptors, *Pharmacological Research* (2020), doi: https://doi.org/10.1016/j.phrs.2020.104879

Vitamin D and advanced glycation end products and their receptors

Running title: Vitamin D and advanced glycation end products

Authors: Sorayya Kheirouri[1†], Mohammad Alizadeh[2]

[1]Ph.D., Professor, Department of Nutrition, Tabriz University of Medical Sciences, Tabriz, Iran

[2]MD, Ph.D., Professor, Student Research center, Tabriz University of Medical Sciences, Tabriz, Iran

[†]Any correspondence to Sorayya Kheirouri, Department of Nutrition, Faculty of Nutrition, Tabriz University of Medical Sciences, Attar Nishabouri St., Tabriz, I. R. Iran. Postal code: 5166614711, POBOX: 14711

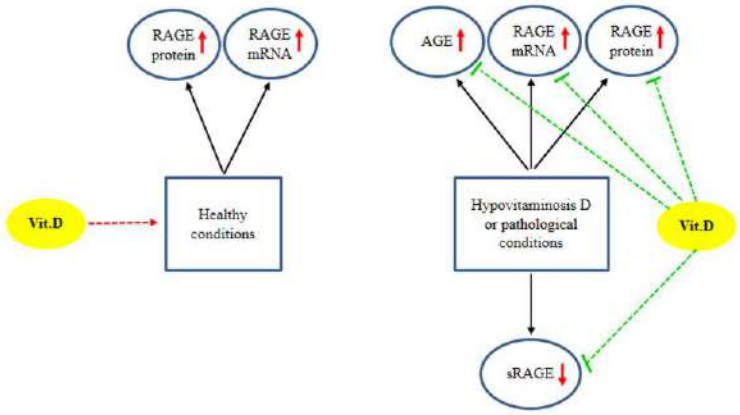
Tel: +98-41-33362117, Fax: +98-41-33340634

Email: Kheirouris@tbzmed.ac.ir

Legends for graphical abstract. A possible mechanistic model for vitamin D effects on AGEs and its receptors

ADAM10A, disintegrin and metalloproteinase domain-containing protein 10; AG2, angiotensin II; AGEs, advanced glycation end products; AT1R, angiotensin II type 1 receptor; IκBα, IkappaBalpha; MAPK, mitogen-activated protein kinase; MMP9, matrix metalloproteinases 9; NF-κB, nuclear factor-kappaB; PKC, protein kinase C; PLC, phospholipase C; RAGE, receptor for AGEs; sRAGE, soluble receptor for AGEs; cRAGE, cleaved RAGE; Vit.D, vitamin D

AGEs bind to RAGE receptor and activate MAPK/NF-κB signaling pathway, which in turn leads to increased RAGE expression. Vitamin D can prevent NF-κB activity by increasing IκBα level. ADAM10 and MMP9 are involved in RAGE shedding and generation of sRAGE. Vitamin D increases ADAM10 expression. Activated AT1R couples to Gq/11 and triggers PLC, and then stimulates PKC. It, thus activates MAPK and leads to increased RAGE expression. Vitamin D decreases AT1R and gene expression of PKC and MAPK.



Study Highlights:

- Vitamin D reduces AGE levels in disease and hypovitaminosis D conditions.
- Vitamin D treatment increases sRAGE level.
- Vitamin D reduces RAGE expression in some disease conditions.
- Vitamin D increases RAGE expression in subjects with normal vitamin D status.

Abstract

Advanced glycation end products (AGEs) are destructive molecules in the body that, at high levels, contribute to the progression of various chronic diseases. Numerous studies have suggested a modifying effect of vitamin D on AGEs and their receptors. This study sought to summarize the effects of vitamin D on AGEs and their receptors, including receptor for AGEs (RAGE) and soluble receptor for AGEs (sRAGE). The search method initially identified 484 articles; 331 remained after duplicate removal. Thirty-five articles were screened and identified as relevant to the study topic. After critical analysis, 27 articles were included in the final analysis. Vitamin D treatment may possibly be beneficial to reduce AGE levels and to augment sRAGE levels, particularly in vitamin D-deficient situations. Treatment with this vitamin may be effective in reducing RAGE expression in some disease conditions, but might be even harmful under normal conditions. The inhibitory or stimulatory effects of vitamin D on AGE receptors are mediated by various signaling pathways, MAPK/NF-κB, ADAM10/MMP9 and AT1R. In populations with chronic diseases and concomitant hypovitaminosis D, vitamin D supplementation can be used as a strategy to ameliorate AGE-mediated complications by modifying the AGE-RAGE and sRAGE systems.

Abbreviations:

ADAM10A, disintegrin and metalloproteinase domain-containing protein 10; AGEs, advanced glycation end products; AGE-FL, AGE-associated fluorescence; AT1R, angiotensin II type 1 receptor; CML, carboxymethyllysine; CVD, cardiovascular diseases; MAPK, mitogen-activated protein kinase; MMP9, matrix metalloproteinases 9; NF-κB, nuclear factor-kappaB; RAGE, receptor for AGEs; SAF, skin autofluorescence; sRAGE, soluble receptor for AGE

Keywords: Vitamin D; calcitriol; AGEs; RAGE; sRAGE; pentosidine; carboxymethyllysine; methylglyoxal; glycation

1. Introduction

Advanced glycation end products (AGEs) are destructive molecules that are irreversibly generated during the glycation process in which carbonyl groups of sugars react non-enzymatically with proteins, lipids or nucleic acids under hyperglycemic conditions in the body [1]. Moreover, AGEs can also be derived from foods. Animal foods such as red meat, sugary foods and highly processed and prepackaged products are rich in AGEs. AGEs can also form during food preparation when certain foods are exposed to high temperatures during grilling, frying or toasting. Diet-derived AGEs play a significant role in the body's AGE pool [2]. High concentrations of AGEs contribute to the development of oxidative stress and inflammation in the body [3] and are associated with the progression of various chronic diseases, including diabetes, cardiovascular diseases (CVD), renal failure, Alzheimer's disease, and premature aging [4-6].

There are two types of AGE receptors. Binding of AGEs to the receptor for advanced glycation end products (RAGE) on the cell membrane leads to intracellular adverse effects such as inflammation, oxidative stress, and apoptosis [7]. Another receptor, named soluble receptor for AGEs (sRAGE), is secreted extracellularly and binds to circulating AGEs, inhibiting the interaction between AGEs and RAGE [8]. This diminishes the harmful intracellular effects of the

AGE-RAGE system. The activated AGE–RAGE signaling cascade has been implicated in the pathogenesis of diverse chronic diseases such as CVD, diabetes, and several cancers [9-12].

Vitamin D is an essential nutrient for health maintenance, with extensive roles that expand over the regulation of calcium and phosphorus metabolism. This vitamin is involved in many biological processes including cell proliferation, differentiation [13], apoptosis [14], immune function and inflammation [15], antioxidant mechanisms [16], antifibrotic processes [17], and neurogenesis [18]. Many professionals consider vitamin D a pro-hormone rather than a common nutritional vitamin. An increasing number of studies have also reported that vitamin D deficiency is closely related to the development of chronic diseases such as CVD, diabetes, cancer, and neurodegenerative and psychiatric diseases [19-21].

Numerous in vitro, animal and human studies have suggested a modifying effect of vitamin D on AGEs and their receptors [22, 23]. However, to our knowledge, there is no review that collates the effects of vitamin D on AGEs and their receptors. Therefore, the research question was as follows: Is vitamin D treatment associated with the levels of AGEs or their receptors (RAGE and sRAGE) in the body? In this regard, this study sought to summarize the effects of vitamin D on AGEs and their receptors.

2. Methods

2.1. Search strategy

This review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (2015 Statement). The PubMed, Google Scholar, Embase, and Scopus databases and Google were searched until March 2020, without date restrictions. Original full-text English-language journal articles were retrieved and observational and clinical studies were included. Reviews, conference papers, abstracts, editorials, and letters were excluded. Articles that investigated the effect or association of vitamin D (not vitamin D receptor) with the production of AGEs or their receptors were included. Studies that assessed the impact of vitamin D on AGE-induced effects such as oxidative stress, inflammation or apoptosis were excluded. The following search terms were used: "vitamin D or 25-hydroxy vitamin D or calcitriol or colecalciferol or calciferol" in the title and "AGEs or pentosidine or carboxymethyllysine or CML or methylglyoxal or MGO or glycation" in the title/abstract.

2.2. *Screening and selection criteria*

The extracted articles were saved in an EndNote file and sorted to remove duplicate reports. The remaining titles and abstracts were screened to identify articles with the correct scope for the

present review. The full texts of the screened articles were then critically analyzed separately for eligibility. Data regarding participant, animal or cell characteristics, study design, intervention method, location, measurement method, and outcomes were extracted.

3. Results

3.1. Study characteristics and selection

As shown in **Fig. 1**, the search method initially retrieved 484 titles and abstracts; 331 articles remained after the elimination of duplicate studies. During the screening stage, 35 studies were found to be relevant to the study topic. During critical analysis of the screened articles, we excluded eight articles because they were not relevant to the study scope (n=4), were not published in English language (n=1), were poster presentations (n=1), reported unclear and contrary results (n=1), or consisted of a study protocol (n=1). Twenty-seven articles that met the criteria of the study were included in the final review and analysis (Fig. 1). The study of Guo et al. [24] was considered two studies since it consisted of two separate in vitro and animal model parts. Therefore, the sum of articles was 28 (5 in vitro, 9 animal and 14 human studies). Eight of the human studies were clinical trials and 6 had a cross-sectional or cohort design.

3.2. Vitamin D and advanced glycation end products

As shown in Table 1, 14 articles including 9 human studies (5 interventional and 4 cross-sectional or cohort) [25-33] and 5 animal studies [22,34-37] investigated the effect of vitamin D treatment on AGEs. Sixty percent of the interventional and experimental studies (6 of 10, 3 animal and 3

human studies) indicated that vitamin D treatment reduced AGE levels [22,23,25,27, 28, 37]. Two of the 5 interventional studies reported no significant changes in the serum levels of AGEs after vitamin D treatment [26,29] (Table 1). Among the cross-sectional or cohort studies, Gradinaru et al. [31] and Chen et al. [30] reported a significant inverse relationship between vitamin D and serum or skin AGE-associated fluorescence. On the other hand, Šebeková et al. [32] indicated that no relationship exists between vitamin D and plasma AGE-associated fluorescence or skin autofluorescence, a marker of AGE accumulation, but there was an inverse correlation with CML levels in diabetic patients (Table 1). Sturmer et al. [33] found no significant relationship between vitamin D and skin autofluorescence, plasma AGE-associated fluorescence or CML in the sample as a whole.

3.3. Vitamin D and receptor for advanced glycation end products (RAGE)

As shown in Table 2, 13 articles including 5 in vitro [24,38-41], 7 animal and one human studies [24, 28, 34-37, 42, 43] evaluated the impact of vitamin D treatment on RAGE protein levels. 84.61% (11 of 13) of the included studies reported a protective effect of vitamin D on RAGE protein or mRNA expression. Seven studies (4 in vitro and 3 animal studies) showed that vitamin D treatment reduced RAGE protein levels [24,34, 38, 39,41-43]; however, two studies (one in vitro and one animal study) found the inverse effect of vitamin D on RAGE protein levels [24,40]. Eight articles investigated RAGE mRNA expression and six reported that vitamin D reduced RAGE mRNA levels [28, 35-37, 39, 43], however, two stated that vitamin D increased RAGE mRNA levels [38,40].

3.4. Vitamin D and soluble receptor for advanced glycation end products (sRAGE)

As shown in Table 3, 10 articles including 7 human studies (4 cross-sectional and 3 interventional) [23,32,33, 44-47], 2 in vitro studies [38,39] and one animal study [48] investigated the impact of

vitamin D on sRAGE levels. All interventional and experimental investigations indicated that vitamin D treatment increased sRAGE levels [23,38,39,44,45, 48]. However, three cross-sectional studies reported no correlation between serum vitamin D and sRAGE level [32,33,47].

4. Discussion

In the present study, we systematically reviewed and summarized the effects of vitamin D on AGEs and their receptors including RAGE and sRAGE.

4.1. Vitamin D and AGEs

Of the 14 articles that examined the effect on or association of vitamin D with AGE levels, only eight studies indicated that vitamin D influences or is inversely associated with AGE levels. Analysis of the included studies suggests that AGE accumulation occurs under conditions of hypovitaminosis D, which has not been addressed by most studies [26,29]. For example, Gradinaru et al. [31] observed higher AGEs in patients with impaired fasting glucose and type 2 diabetes who had lower vitamin D levels. Therefore, vitamin D treatment will be effective in attenuating AGE levels in the presence of vitamin D deficiency and AGE accumulation. Another issue that should be considered is that most of the studies did not measure tissue or circulating levels of specific members of the AGE group but instead evaluated tissue autofluorescence or circulating fluorescent components, which may not truly represent AGE levels. For example, in the study of Sebekova et al. [32], vitamin D was not associated with plasma AGE-associated fluorescence or skin autofluorescence, but was correlated significantly with the levels of CML, a member of the AGE

group. Thus, this warrants further clinical trials to assess the effect of vitamin D supplementation on specific AGE components.

4.2. Vitamin D and RAGE

A protective effect of vitamin D on RAGE protein or mRNA expression was reported by 84.61% (11 of 13) of the included studies. However, two studies found an inverse effect of vitamin D on RAGE protein and mRNA expression. Although the lack of similarity among the included studies impaired comparison of the findings, however, the observed inconsistency across the studies may not possibly be related to the form / dose of vitamin D used or measurement methods of RAGE, because varying findings has been reported for same form/dose of vitamin D [24,39,40] or same measurement method of RAGE [38,40] by different studies. The type of cells used and especially the physiological condition of the animals (normal vs. diseased) are possible contributors to the discrepancy. A disease condition may affect the efficacy of vitamin D supplementation and the association might differ between healthy and disease conditions. It appears that vitamin D exposure enhances RAGE expression under normal conditions. For example, the studies of Benetti et al. [34], Lee et al. [42] and Sturza et al. [41] that reported reduced levels of RAGE after vitamin D treatment used obese and diabetic animals or cells, while normal animals or cells were used in the studies of Guo et al. [24] and Rüster et al. [40] that showed increased levels of RAGE after vitamin D treatment. Collectively, vitamin D treatment may be effective in reducing RAGE expression under pathological conditions, but might be even harmful under normal conditions.

4.3. Vitamin D and sRAGE

The findings of this review showed that vitamin D treatment increases sRAGE levels. However, several cross-sectional studies did not find any association between circulating vitamin D status and sRAGE levels. These cross-sectional investigations were conducted on healthy populations or

on patients with vitamin D and sRAGE levels comparable to those of healthy people [32,33,47], a fact that might have attenuated the associations. In all clinical trials in which vitamin D treatment enhanced sRAGE levels, the population recruited was either vitamin D deficient or had a specific disease condition [23,44,45,48]. For instance, in the study of Garg et al. [46], vitamin D was associated with sRAGE in women with polycystic ovary syndrome. Taken together, vitamin D treatment may possibly be beneficial to increase sRAGE levels in subjects with hypovitaminosis D and unhealthy status.

4.4. Mechanistic pathways underlying the inhibitory effect of vitamin D on the expression of AGEs

4.4.1. Mitogen-activated protein kinase (MAPK) and nuclear factor-κB (NF-κB) pathways

RAGE activation by its ligand, AGEs, enhances the generation of more RAGE. Upon binding of AGEs to RAGE, several cellular signaling pathways including the MAPK/NF-κB pathway are activated (**Fig. 2**). This activation, in turn, increases the production of inflammatory mediators, oxidative stress, and RAGE expression [49,50]. Furthermore, vitamin D can prevent NF-κB activity, a positive regulator of RAGE expression, by increasing the levels of IkappaBalpha, a potent NFkappaB inhibitor [51]. Benetti et al. [34] assessed the effects of vitamin D treatment on the activation of NF-κB in gastrocnemius homogenates and reported that vitamin D significantly reduced NF-κB activation (Fig. 2).

4.4.2. A disintegrin and metalloproteinase domain-containing protein 10 (ADAM10) and matrix metalloproteinases 9 (MMP9) pathways

ADAM10 is a cell surface protein that mainly cleaves membrane proteins and then releases soluble ectodomains with altered location and function [52,53]. As shown in Fig. 2, ADAM10 and MMP9 have been implicated in RAGE shedding and generation of sRAGE [54,55]. sRAGE is a shortened form of full-length RAGE that lacks the transmembrane domain, which is isolated by ADAM10.

Once released, sRAGE can bind to AGEs and inhibits their binding to membrane RAGE. Lee et al. [38] reported that calcitriol reduces RAGE, enhances sRAGE protein and mRNA expression, and also increases ADAM10 expression. According to these authors, calcitriol suppresses RAGE through ADAM10 activation [38].

4.4.3. Angiotensin II type I receptor pathway

Stimulation of angiotensin II type 1 receptor (AT1R) has been demonstrated to upregulate the RAGE pathway [56]. AT1R is a plasma membrane receptor that is activated by angiotensin II as its ligand. The activated receptor couples to heterotrimeric G protein of Gq/11 and triggers phospholipase C. The latter induces protein kinase C [57], which activates MAPK [58,59], finally increasing RAGE expression. Calcitriol has been reported to decrease AT1R [42,60]. Furthermore, Haddad Kashani et al. [61] showed that vitamin D supplementation decreases gene expression of protein kinase C and MAPK in peripheral blood mononuclear cells of diabetic patients (Fig. 2).

4.4.4. Conclusions and future outlooks

Vitamin D treatment may possibly be beneficial to reduce AGE levels and to augment sRAGE levels in vitamin D-deficient and pathological conditions. Treatment with this vitamin may be effective in reducing RAGE expression under some pathological conditions, but might be even harmful under normal conditions. The inhibitory or stimulatory effects of vitamin D on AGE receptors are mediated by various signaling pathways, MAPK/NF-κB, ADAM10/MMP9 and AT1R. Most of the reviewed studies used cells, tissues, animals or human subjects with normal or unclear vitamin D status. Thus, to assess the effect of vitamin D on the levels of AGEs or their receptors, future interventional studies are required to evaluate situations where vitamin D deficiency is occurring. Furthermore, none of the included clinical trials focused on specific

members of the AGE group. Therefore, further clinical trials are necessary to assess the effect of vitamin D supplementation on the tissue or circulating levels of specific members of the AGE group such as N(6)-carboxymethyllysine, pentosidine and methylglyoxal as markers of AGEs.

4.4.5. Strengths and limitations of the study

The included studies were conducted in different countries across the world and were relatively recent. Most of the studies did not measure tissue or circulating specific AGEs but instead evaluated tissue autofluorescence or circulating fluorescent components as markers of total AGE accumulation, which may not truly represent AGE levels. Furthermore, the included studies were heterogenous with respect to condition or type of cells, animals and human participants recruited (normal or pathological condition), form/dose of vitamin D used, and measurement methods. This lack of similarity among the included studies impaired comparison of the findings.

4.4.6. Application of the findings

In populations with chronic diseases and concomitant hypovitaminosis D, vitamin D supplementation can be used as a cost-effective strategy to ameliorate AGE-mediated complications by modifying the AGE-RAGE and sRAGE systems.

Conflict of interest: The authors have declared that no conflict of interest exists.

Funding support: There was no financial support for this study.

Acknowledgment

There is no acknowledgment. Both authors, SK and MA, have read and approved the manuscript.

References

[1] Wei Q, Liu T, Sun DW. 2018. Advanced glycation end-products (AGEs) in foods and their detecting techniques and methods: A review. Trends Food Sci Technol. 82(2018), 32-45 https://doi.org/10.1016/j.tifs.2018.09.020

[2] Uribarri J, Woodruff S, Goodman S, Cai W, Chen X, Pyzik R, Yong A, Striker GE, Vlassara H. Advanced glycation end products in foods and a practical guide to their reduction in the diet, J. Am. Diet Assoc. 110 (6) (2010) 911-916.e12, doi: 10.1016/j.jada.2010.03.018.

[3] Uribarri J, Cai W, Peppa M, Goodman S, Ferrucci L, Striker G, Vlassara H. Circulating glycotoxins and dietary advanced glycation endproducts: two links to inflammatory response, oxidative stress, and aging, J. Gerontol. A Biol. Sci. Med. Sci. 62 (4) (2007) 427-433.

[4] Semba RD, Ferrucci L, Sun K, Beck J, Dalal M, Varadhan R, Walston J, Guralnik JM, Fried LP. Advanced glycation end products and their circulating receptors predict cardiovascular disease mortality in older community-dwelling women, Aging Clin. Exp. Res. 21 (2) (2009) 182-190.

[5] Bohlender JM, Franke S, Stein G, Wolf G. Advanced glycation end products and the kidney, Am. J. Physiol. Renal Physiol. 289 (4) (2005) F645-659.

[6] Srikanth V, Maczurek A, Phan T, Steele M, Westcott B, Juskiw D, Münch G. 2011. Advanced glycation endproducts and their receptor RAGE in Alzheimer's disease. Neurobiol Aging. 32(5):763-777. doi: 10.1016/j.neurobiolaging.2009.04.016.

[7] Schmidt AM, Yan SD, Wautier JL, Stern D. 1999. Activation of receptor for advanced glycation end products: a mechanism for chronic vascular dysfunction in diabetic vasculopathy and atherosclerosis. Circ Res. 84(5):489-497.

[8] Geroldi D, Falcone C, Emanuele E. 2006. Soluble receptor for advanced glycation end products: from disease marker to potential therapeutic target. Curr Med Chem. 13(17):1971-1978.

[9] Kay AM, Simpson CL, Stewart JA Jr. 2016. The Role of AGE/RAGE Signaling in Diabetes-Mediated Vascular Calcification. J Diabetes Res. 2016:6809703. doi: 10.1155/2016/6809703.

[10] Senatus LM, Schmidt AM. 2017. The AGE-RAGE Axis: Implications for Age-Associated Arterial Diseases. Front Genet. 8:187. doi: 10.3389/fgene.2017.00187

[11] Bao JM, He MY, Liu YW, Lu YJ, Hong YQ, Luo HH, Ren ZL, Zhao SC, Jiang Y. 2015. AGE/RAGE/Akt pathway contributes to prostate cancer cell proliferation by promoting Rb phosphorylation and degradation. Am J Cancer Res. 5(5):1741-1750.

[12] Yamagishi S, Matsui T, Fukami K. 2015. Role of receptor for advanced glycation end products (RAGE) and its ligands in cancer risk. Rejuvenation Res. 18(1):48-56. doi: 10.1089/rej.2014.1625.

[13] Samuel S, Sitrin MD. 2008. Vitamin D's role in cell proliferation and differentiation. Nutr Rev. 66(10 Suppl 2):S116-124. doi: 10.1111/j.1753-4887.2008.00094.x.

[14] Tabasi N, Rastin M, Mahmoudi M, Ghoryani M, Mirfeizi Z, Rabe SZ, Reihani H. 2015. Influence of vitamin D on cell cycle, apoptosis, and some apoptosis related molecules in systemic lupus erythematosus. Iran J Basic Med Sci. 18(11):1107-1111.

[15] Querfeld U. 2013. Vitamin D and inflammation. Pediatr Nephrol. 28(4):605-610. doi: 10.1007/s00467-012-2377-4.

[16] Dhas Y, Mishra N1, Banerjee J. 2017. Vitamin D deficiency and oxidative stress in type 2 diabetic population of India. Cardiovasc Hematol Agents Med Chem. 14(2):82-89. doi: 10.2174/1871525714666160426150233.

[17] Dadabhai AS, Saberi B, Lobner K, Shinohara RT, Mullin GE. 2017. Influence of vitamin D on liver fibrosis in chronic hepatitis C: A systematic review and meta-analysis of the pooled clinical trials data. World J Hepatol. 9(5):278-287. doi: 10.4254/wjh.v9.i5.278.

[18] Groves NJ, Burne THJ. 2017. The impact of vitamin D deficiency on neurogenesis in the adult brain. Neural Regen Res. 12(3):393-394. doi: 10.4103/1673-5374.202936.

[19] Baz-Hecht M, Goldfine AB. 2010. The impact of vitamin D deficiency on diabetes and cardiovascular risk. Curr Opin Endocrinol Diabetes Obes. 17(2):113-119. doi: 10.1097/MED.0b013e3283372859.

[20] Dana-Alamdari L, Kheirouri S, Noorazar SG. 2015. Serum 25-Hydroxyvitamin D in Patients with Major Depressive Disorder. Iran J Public Health. 44(5):690-697.

[21] Littlejohns TJ, Henley WE, Lang IA, Annweiler C, Beauchet O, Chaves PH, Fried L, Kestenbaum BR, Kuller LH, Langa KM, et al. 2014. Vitamin D and the risk of dementia and Alzheimer disease. Neurology. 83(10):920-928. doi: 10.1212/WNL.0000000000000755.

[22] Salum E, Kals J, Kampus P, Salum T, Zilmer K, Aunapuu M, Arend A, Eha J, Zilmer M. 2013. Vitamin D reduces deposition of advanced glycation end-products in the aortic wall and systemic oxidative stress in diabetic rats. Diabetes Res Clin Pract. 100(2):243–249.

[23] Sung JY, Chung W, Kim AJ, Kim HS, Ro H, Chang JH, Lee HH, Jung JY. 2013. Calcitriol treatment increases serum levels of the soluble receptor of advanced glycation end products

in hemodialysis patients with secondary hyperparathyroidism. Tohoku J Exp Med. 230(1):59–66.

[24] Guo YX, He LY, Zhang M, Wang F, Liu F, Peng WX. 2016. 1,25-Dihydroxyvitamin D3 regulates expression of LRP1 and RAGE in vitro and in vivo, enhancing Aβ1-40 brain-to-blood efflux and peripheral uptake transport. Neuroscience. 322:28-38. doi: 10.1016/j.neuroscience.2016.01.041.

[25] Dreyer G, Tucker AT, Harwood SM, Pearse RM, Raftery MJ, Yaqoob MM. 2014. Ergocalciferol and microcirculatory function in chronic kidney disease and concomitant vitamin d deficiency: an exploratory, double blind, randomised controlled trial. PLoS One. 9(7):e99461. doi: 10.1371/journal.pone.0099461.

[26] Krul-Poel YH, Agca R, Lips P, van Wijland H, Stam F, Simsek S. 2015. Vitamin D status is associated with skin autofluorescence in patients with type 2 diabetes mellitus: a preliminary report. Cardiovasc Diabetol. 14:89. doi: 10.1186/s12933-015-0250-z.

[27] Nikooyeh B, Neyestani TR, Tayebinejad N, Alavi-Majd H, Shariatzadeh N, Kalayi A, Zahedirad M, Heravifard S, Salekzamani S. 2014. Daily intake of vitamin D- or calcium-vitamin D-fortified Persian yogurt drink (doogh) attenuates diabetes-induced oxidative stress: evidence for antioxidative properties of vitamin D. J Hum Nutr Diet. 27 Suppl 2:276-283. doi: 10.1111/jhn.12142.

[28] Omidian M, Djalali M, Javanbakht MH, Eshraghian MR, Abshirini M, Omidian P, Alvandi E, Mahmoudi M. Effects of vitamin D supplementation on advanced glycation end products signaling pathway in T2DM patients: a randomized, placebo-controlled, double blind clinical trial. Diabetol Metab Syndr. 2019;11:86. doi: 10.1186/s13098-019-0479-x.

[29] Tanaka M, Tokunaga K, Komaba H, Itoh K, Matsushita K, Watanabe H, Kadowaki D, Maruyama T, Otagiri M, Fukagawa M. 2011. Vitamin D receptor activator reduces oxidative stress in hemodialysis patients with secondary hyperparathyroidism. Ther Apher Dial. 15(2):161-168. doi: 10.1111/j.1744-9987.2010.00890.x.

[30] Chen J, van der Duin D, Campos-Obando N, Ikram MA, Nijsten TEC, Uitterlinden AG, Zillikens MC. Serum 25-hydroxyvitamin D3 is associated with advanced glycation end products (AGEs) measured as skin autofluorescence: The Rotterdam Study. Eur J Epidemiol. 2019;34(1):67-77. doi: 10.1007/s10654-018-0444-2.

[31] Gradinaru D, Borsa C, Ionescu C, Margina D, Prada GI, Jansen E. 2012. Vitamin D status and oxidative stress markers in the elderly with impaired fasting glucose and type 2 diabetes mellitus. Aging Clin Exp Res. 24(6):595-602. doi: 10.3275/8591.

[32] Šebeková K, Stürmer M, Fazeli G, Bahner U, Stäb F, Heidland A. 2015. Is vitamin D deficiency related to accumulation of advanced glycation end products, markers of inflammation, and oxidative stress in diabetic subjects? Biomed Res Int. 2015:958097. doi: 10.1155/2015/958097.

[33] Stürmer M, Šebeková K, Fazeli G, Bahner U, Stäb F, Heidland A. 2015. 25-hydroxyvitamin d and advanced glycation endproducts in healthy and hypertensive subjects: are there interactions? J Ren Nutr. 25(2):209-216. doi: 10.1053/j.jrn.2014.10.027.

[34] Benetti E, Mastrocola R, Chiazza F, Nigro D, D'Antona G, Bordano V, Fantozzi R, Aragno M, Collino M, Minetto MA. 2018. Effects of vitamin D on insulin resistance and myosteatosis in diet-induced obese mice. PLoS One. 13(1):e0189707. doi: 10.1371/journal.pone.0189707.

[35] Derakhshanian H, Djalali M, Mohammad Hassan MH, Alvandi E, Eshraghian MR, Mirshafiey A, Nadimi H, Jahanabadi S, Zarei M, Djazayery A. Vitamin D suppresses cellular pathways of diabetes complication in liver. Iran J Basic Med Sci. 2019;22(6):690-694. doi: 10.22038/ijbms.2019.36054.8584.

[36] Derakhshanian H, Djazayery A, Javanbakht MH, Eshraghian MR, Mirshafiey A, Jahanabadi S, Ghadbeigi S, Zarei M, Alvandi E, Djalali M. Vitamin D downregulates key genes of diabetes complications in cardiomyocyte. J Cell Physiol. 2019;1–7. DOI: 10.1002/jcp.28743

[37] Jeremy M, Gurusubramanian G, Roy VK. Vitamin D3 regulates apoptosis and proliferation in the testis of D-galactose-induced aged rat model. Scientific Reports 2019;9:14103 https://doi.org/10.1038/s41598-019-50679-y

[38] Lee TW, Kao YH, Lee TI, Chen YJ. 2017. ADAM10 modulates calcitriol-regulated RAGE in cardiomyocytes. Eur J Clin Invest. 47(9):675-683. doi: 10.1111/eci.12789.

[39] Merhi Z, Buyuk E, Cipolla MJ. 2018. Advanced glycation end products alter steroidogenic gene expression by granulosa cells: an effect partially reversible by vitamin D. Mol Hum Reprod. 24(6):318-326. doi: 10.1093/molehr/gay014.

[40] Rüster C, Franke S, Reuter S, Mrowka R, Bondeva T, Wolf G. 2016. Vitamin D3 partly antagonizes advanced-glycation endproducts-induced NFκB activation in mouse podocytes. Nephron. 134(2):105-116.

[41] Sturza A, Duicu O, Vaduva A, Noveanu L, Danila M, Privistirescu A, Timar R, Muntean D, Munteanu M. 2015. Reduction of RAGE expression by vitamin D in isolated diabetic rat aortas. Revista de Chimie (Bucharest). 66(9):1509-1512 http://www.revistadechimie.ro

[42] Lee TW, Kao YH, Lee TI, Chang CJ, Lien GS, Chen YJ. 2014. Calcitriol modulates receptor for advanced glycation end products (RAGE) in diabetic hearts. Int J Cardiol. 173(2):236-241. doi: 10.1016/j.ijcard.2014.02.041.

[43] Xu ML, Yu XJ, Zhao JQ, Du Y, Xia WJ, Su Q, Du MM, Yang Q, Qi J, Li Y, Zhou SW, Zhu GQ, Li HB, Kang YM. Calcitriol ameliorated autonomic dysfunction and hypertension by down-regulating inflammation and oxidative stress in the paraventricular nucleus of SHR. Toxicol Appl Pharmacol. 2020;394:114950. doi: 10.1016/j.taap.2020.114950.

[44] Irani M, Minkoff H, Seifer DB, Merhi Z. 2014. Vitamin D increases serum levels of the soluble receptor for advanced glycation end products in women with PCOS. J Clin Endocrinol Metab. 99(5):E886-890. doi: 10.1210/jc.2013-4374.

[45] Kubiak J, Thorsby PM, Kamycheva E, Jorde R. 2018. Vitamin D supplementation does not improve CVD risk factors in vitamin D-insufficient subjects. Endocr Connect. 7(6):840-849. doi: 10.1530/EC-18-0144.

[46] Garg D, Grazi R, Lambert-Messerlian GM, Merhi Z. 2017. Correlation between follicular fluid levels of sRAGE and vitamin D in women with PCOS. J Assist Reprod Genet. 34(11):1507-1513. doi: 10.1007/s10815-017-1011-6.

[47] Mayer O, Seidlerová J, Černá V, Kučerová A, Karnosová P, Hronová M, Wohlfahrt P, Fuchsová R, Filipovský J, Cífková R, et al. 2018. Serum vitamin D status, vitamin D receptor polymorphism, and glucose homeostasis in healthy subjects. Horm Metab Res. 50(1):56-64. doi: 10.1055/s-0043-122144.

[48] Mohammed NA, El-Malkey NF, Ibrahim AA, Abdullah DM. Vitamin D3 supplementation ameliorates ovariectomy-induced cardiac apoptotic and structural changes in adult albino rats. Can J Physiol Pharmacol. 2019;97(7):647-654. doi: 10.1139/cjpp-2018-0674.

[49] Bierhaus A, Humpert PM, Morcos M, Wendt T, Chavakis T, Arnold B, Stern DM, Nawroth PP. 2005. Understanding RAGE, the receptor for advanced glycation end products. J Mol Med (Berl). 83(11):876-886.

[50] Alexiou P, Chatzopoulou M, Pegklidou K, Demopoulos VJ. 2010. RAGE: a multi-ligand receptor unveiling novel insights in health and disease. Curr Med Chem. 17(21):2232-2252.

[51] Cohen-Lahav M, Shany S, Tobvin D, Chaimovitz C, Douvdevani A. 2006. Vitamin D decreases NFkappaB activity by increasing IkappaBalpha levels. Nephrol Dial Transplant. 21(4):889-897.

[52] Nagano O, Saya H. 2004. Mechanism and biological significance of CD44 cleavage. Cancer Sci. 95(12):930–935. doi:10.1111/j.1349-7006.2004.tb03179.x.

[53] Blobel CP. 2005. ADAMs: key components in EGFR signalling and development. Nat Rev Mol Cell Biol. 6(1):32-43. doi:10.1038/nrm1548.

[54] Zhang L, Bukulin M, Kojro E, Roth A, Metz VV, Fahrenholz F, Nawroth PP, Bierhaus A, Postina R. 2008. Receptor for advanced glycation end products is subjected to protein ectodomain shedding by metalloproteinases. J Biol Chem. 283(51):35507-35516. doi: 10.1074/jbc.M806948200.

[55] Lee AC, Lam JK, Shiu SW, Wong Y, Betteridge DJ, Tan KC. 2015. Serum level of soluble receptor for advanced glycation end products is associated with A disintegrin and metalloproteinase 10 in type 1 diabetes. PLoS One. 10(9):e0137330. doi: 10.1371/journal.pone.0137330.

[56] Ihara Y, Egashira K, Nakano K, Ohtani K, Kubo M, Koga J, Iwai M, Horiuchi M, Gang Z, Yamagishi S, Sunagawa K. 2007. Upregulation of the ligand-RAGE pathway via the

angiotensin II type I receptor is essential in the pathogenesis of diabetic atherosclerosis. J Mol Cell Cardiol. 43(4):455-464.

[57] Higuchi S, Ohtsu H, Suzuki H, Shirai H, Frank GD, Eguchi S. 2007. Angiotensin II signal transduction through the AT1 receptor: novel insights into mechanisms and pathophysiology. Clin Sci (Lond). 112(8):417-428.

[58] Tian Y, Smith RD, Balla T, Catt KJ. 1998. Angiotensin II activates mitogen-activated protein kinase via protein kinase C and Ras/Raf-1 kinase in bovine adrenal glomerulosa cells. Endocrinology. 139(4):1801-1809.

[59] VanRenterghem B, Browning MD, Maller JL. 1994. Regulation of mitogen-activated protein kinase activation by protein kinases A and C in a cell-free system. J Biol Chem. 269(40):24666-24672.

[60] Dong J, Wong SL, Lau CW, Lee HK, Ng CF, Zhang L, Yao X, Chen ZY, Vanhoutte PM, Huang Y. 2012. Calcitriol protects renovascular function in hypertension by down-regulating angiotensin II type 1 receptors and reducing oxidative stress. Eur Heart J. 33(23):2980-2990. doi: 10.1093/eurheartj/ehr459.

[61] Haddad Kashani H, Seyed Hosseini E, Nikzad H, Soleimani A, Soleimani M, Tamadon MR, Keneshlou F, Asemi Z. 2018. The effects of vitamin D supplementation on signaling pathway of inflammation and oxidative stress in diabetic hemodialysis: A randomized, double-blind, placebo-controlled trial. Front Pharmacol. 9:50. doi: 10.3389/fphar.2018.00050.

Legends for figures

Figure 1. Flow diagram of the study

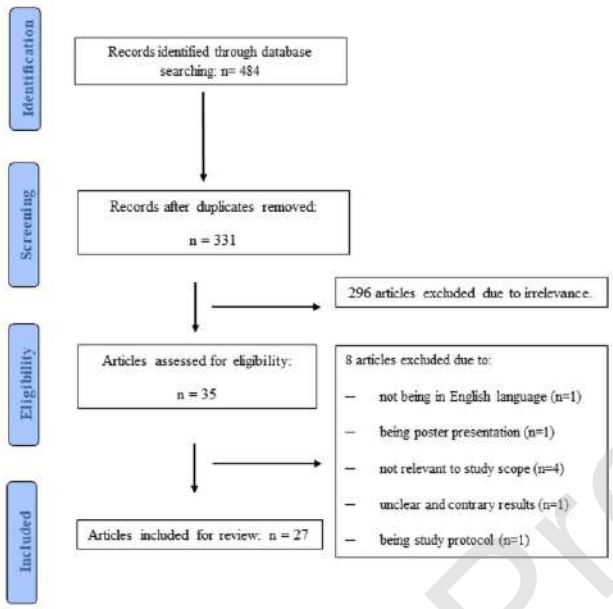


Figure 2. Effect of Vitamin D on AGEs, RAGE and sRAGE

Vitamin D treatment inhibits the increase of AGEs, RAGE and decrease of sRAGE levels under vitamin D-deficient and pathological conditions. Vitamin D treatment increases RAGE protein and mRNA levels under normal conditions.

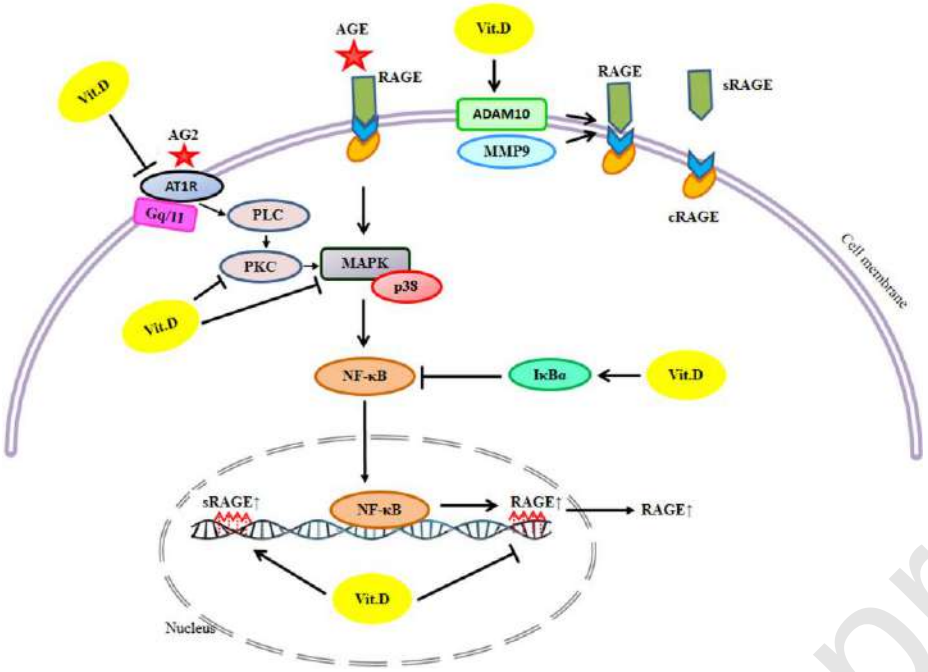


Table 1. Summary table of vitamin D effects on AGEs levels

Type of study	Author/ date	Country	Participants/animals and method of intervention	Location and method of measurement	Results
Human/ Clinical trial	Dreyer et al./2014 [25]	UK	14 patients with non-diabetic chronic kidney disease and concomitant vitamin D deficiency received oral ergocalciferol (50,000 IU weekly for one month followed by 50,000 IU monthly) or placebo (n=15), over 6 months.	Skin	AT: Tissue SAF ↓ (p=0.03)
	Krul-Poel et al./ 2015[26]	Netherlands	245 patients with type 2 diabetes mellitus (67 ± 8 years) received either vitamin D 50,000 IU/month (n=107) or placebo (n=103) for 6 months.	Skin	In patients with a serum 25(OH)D ≥70 nmol/l: SAF↓ Serum 25(OH)D ↔ SAF (β= −0.006, p<0.001) AT: SAF Θ
	Nikooyeh et al./ 2014[27]	Iran	90 patients with type 2 diabetes aged 30–50 years were instructed to drink two 250-mL bottles of doogh a day as follows: 150 mg calcium per 250 mL of doogh (PD, n=30) 150 mg calcium + 500 IU vitamin D per 250 mL of doogh (DD, n=30)	Serum	In both DD and CDD groups: Serum 25(OH)D↑ In both DD and CDD groups: Within-group protein carbonyl↓ Changes of AGEs levels differed among DD, CDD and PD groups (p=0.003).

			250 mg calcium + 500 IU vitamin D per 250 mL of doogh (CDD, n=30)		
	Omidian et al./2019[28]	Iran	Patients with type-2 diabetic (n=48) received 100µg vitamin D or placebo for 3 months.	Serum	Vitamin D serum level increased in vitamin D group ($p < 0.001$). AT: AGEs level ↓ ($p=0.001$).
	Tanaka et al./2011[29]	Japan	Hemodialysis patients with secondary hyperparathyroidism (n=11) were treated with 1.5 mg/week calcitriol for four weeks.	Serum	AT: AGE products Θ
Human/ Cohort or Cross-sectional	Chen et al./2019[30]	Netherlands	Community-dwelling participants (n=2746), age ≥ 45 years	Skin	Serum $25(OH)D_3$ ↔ inversely SAF ($p<0.0001$)
	Gradinaru et al./ 2012[31]	Romania	Elderly subjects with impaired glucose metabolism/n=90 /65-78 years	Serum/ Spectrofluorimetrically	25(OH)D ↔ inversely AGEs ($p<0.001$) Groups with impaired fasting glucose and type 2 diabetes had lower vitamin D level and higher AGEs.

	Šebeková et al./ 2015[32]	Germany	276 diabetic subjects (43 T1DM and 233 T2DM) and 121 nondiabetic controls aged 65.0 ± 13.4 years were studied.	Skin and plasma/ CML: ELISA	In diabetics: SAF and AGE-Fl ↑ 25(OH)D level was same in diabetics and non-diabetics. In diabetics: 25(OH)D ≠ AGE-Fl & SAF In diabetics: CML ↔ 25(OH)D (r=−0.197, p=0.006)
	Sturmer et al./2015[33]	Germany	146 subjects (119 healthy persons and 27 hypertensive patients) aged 57.0 ±15.5 years were studied.	Skin and plasma	In the whole cohort: vitamin D3 ≠ SAF, plasma AGE-Fl and CML Mean vitamin D levels was not different between smokers and nonsmokers. Among smokers: vitamin D3 ↔ inversely plasma AGE-F1 (r=−0.551, p=0.049)
Animal	Benetti et al./2018[34]	Italy	Male obese mice (n=40, 4 weeks old) were treated with 1,25-dihydroxycholecalciferol (7 µg.kg-1, three times/week) for 2 months.	Gastrocnemious muscle/ Western blotting	AT: CML ↓
	Derakhshanian et al./2019[35]	Iran	Diabetic rats (n=8, each group) were treated for four weeks with placebo or vitamin D (two intramuscular injections of 20000 IU/kg).	Liver/ ELISA	Vitamin D injection increased plasma level of 25-hydroxycholecalciferol (p=0.005). AT: AGE levels Θ
	Derakhshanian et al./2019[36]	Iran	Diabetic rats (n=8, each group) were treated for four weeks with placebo or vitamin D	Serum and cardiac myocytes/ ELISA	AGEs levels increased in serum and heart samples of diabetic rats.

			(two intramuscular injections of 20000 IU/kg).		AT: AGE levels Θ
	Jeremy et al./2019[37]	India	Healthy male rats (n=6 in each group), 3–4 months old were treated with 40 or 400IU/kg vitamin D3 with or without D-galactose (120 mg/Kg).	Serum and intratesticular/ELISA	Serum and intra-testicular levels of AGE was higher in aged rats ($p < 0.05$). AT: AGE ↓
	Salum et al./2013[22]	Estonia	Male diabetic rats (n=8, age 4 months) were treated with cholecalciferol (500 IU/kg) Orally for 10 weeks.	Aortic wall / ELISA	Untreated diabetic rats: CML↑ AT: CML↓
AGEs, advanced glycation end products; AGE-Fl, AGE associated fluorescence; AT, after treatment; CML, carboxymethyl lysine; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; SAF, skin autofluorescence; Θ represents no significant change; ↔ represent presence of correlation; ≠ represent no significant relationship Vitamin D treatment attenuates AGE levels in the presence of vitamin D deficiency and AGE accumulation.					

Table 2. Summary table of vitamin D effects on formation of RAGE

	Author/date	Country	Type of cells or animals studied/ number and age of animals	Vitamin D type / dosage	Duration and method of treatment	Method and location of measurement	Results
In-vitro	Guo et al./ 2016[24]	China	Mouse blood–brain barrier model	1,25$(OH)_2D_3$ / 2.5 µg/kg/day	14 days	Immunofluorescence/ blood–brain barrier model	AT: RAGE protein ↓
	Lee et al./ 2017[38]	Taiwan	Mouse cardiomyocytes	Calcitriol / 10 and 100 nM	48 h	Protein; Western blot mRNA; PCR	AT: RAGE protein ↓ ($p<0.01$) RAGE mRNA expression ↑ ($p<0.01$)
	Merhi et al./ 2018[39]	USA	Granulosa cells from women who were undergoing in-vitro fertilization	Vit D3 / 100 nM	24 h	Immunofluorescence	AT: RAGE mRNA ↓ (33%) RAGE protein ↓ (44%) ($p<0.05$)
	Rüster et al./ 2016[40]	Germany	Mice podocytes	Vit D3 /100, 500 pmol/l or Paricalcitol / 5,000 pmol/l	24 h	mRNA; real-time PCR Protein; western blotting	AT: RAGE mRNA and protein expression ↑
	Sturza et al./ 2015[41]	Romania	Diabetic rat aortic sample	1,25VitD3 / 0.1 µM	12 h	immunohistochemistry	BT: RAGE ↑ AT: RAGE ↓

Animal	Benetti et al./ 2018[34]	Italy	Male mice model of diet-induced insulin resistance, n=40, 4 weeks old	1,25-dihydroxycholecalciferol / 7 μg.kg-1	Dietary, Three times per week for 2 months	Western blotting/ Gastrocnemious muscle	AT: RAGE protein ↓
	Derakhshanian et al./2019[35]	Iran	Male diabetic rats (n=8, each group), aged 3-4 months	20000 IU/kg vitamin D or placebo	Intramuscular injection, two times on the 1st and 14th days of diabetes development	Real-time PCR	Expression of RAGE mRNA increased in liver of diabetic group ($p<0.001$). AT: RAGE mRNA ↓
	Derakhshanian et al./2019[36]	Iran	Male diabetic rats (n=8, each group), aged 3-4 months	20000 IU/kg vitamin D or placebo	Intramuscular injection, two times on the 1st and 14th days of diabetes development	Real-time PCR	In cardiac myocytes, AT: RAGE mRNA ↓
	Jeremy et al./2019[37]	India	Male aged rats (n=6 in each group), 3–4 months old	40 or 400IU/kg vitamin D3 with or without D-galactose (120 mg/Kg)	D-galactose was given for 42 consecutive days and vitamin D3 treatment was given twice weekly for 6 weeks.	Western blotting/ Testis	RAGE expression was higher in testis of normal and D-gal-induced aged rats ($p < 0.05$). AT: RAGE mRNA ↓

	Guo et al./ 2016[24]	China	Male mice, n=18	1,25$(OH)_2D_3$ / 2.5 µg/kg/day	Intraperitoneally, 14 days	Immunohistochemical method/ Microvascular endothelial cells of mice hippocampus	AT: RAGE protein ↑
	Lee et al./ 2014[42]	Taiwan	Male diabetic rats, n=9, 12 weeks old	Calcitriol / 150 ng/kg/day	Subcutaneously, 4 weeks	Western blot/ Cardiac	AT: RAGE protein ↓
	Xu et al./2020[43]	China	Male hypertensive and normotensive rats	calcitriol (40 ng/day) or vehicle (0.11 µL/h)	Chronic infusion through hypothalamic paraventricular nucleus for 4 weeks	Real-time RT-PCR/ Hypothalamic paraventricular nucleus and left ventricular tissues	mRNA and protein expression levels RAGE was higher in hypertensive rats. AT: RAGE mRNA and protein ↓
Human	Omidian et al./2019[28]	Iran	Patients with type-2 diabetic (n=48)	100µg vitamin D or placebo	Oral supplementation, 3 months	Real‑ time PCR/ Peripheral blood mononuclear cells	AT: RAGE mRNA ↓ (p=0.001)
RAGE, receptor for advanced glycation end products; BT, before treatment; AT, after treatment Vitamin D treatment reduces RAGE expression under pathological conditions, but enhances it under normal conditions.							

Table 3. Summary table of vitamin D effects on sRAGE levels

Type of study	Author/date	Country	Participants/cells and method of intervention	Location and method of measurement	Results
Human/ Clinical trial	Irani et al./2014[44]	USA	51 vitamin D-deficient women were treated with 50000 IU oral vitamin D3 once weekly for 8 weeks (16 with PCOS and 35 controls) and 16 women were not treated (six with PCOS and 10 controls).	Serum / ELISA	AT, in women with and without PCOS: Serum 25(OH)D ↑ ($p<0.0001$) In women with PCOS: Serum sRAGE ↑ ($p=0.03$) In women with PCOS: Serum sRAGE ↑ ↔ serum 25(OH)D ↑ ($r= 0.6$, $p=0 .01$)
	Kubiak et al./2018[45]	Norway	411 vitamin D-insufficient subjects aged < 80 years treated orally with high-dose vitamin D (100,000 IU loading dose, followed by 20,000 IU/week) (n=208) or placebo (n=203) for 4-months.	Serum / ELISA	In vitamin D group: Serum 25(OH)D ↑, Delta sRAGE ↑ ($p<0.05$)
	Sung et al./2013[23]	Korea	Hemodialysis patients with secondary hyperparathyroidism (n=51, 52.6 ± 14.7 years) who had low serum 1,25 dihydroxyvitamin D3 (1,25D) levels and elevated intact parathyroid hormone levels was administered intravenous calcitriol (2	Serum/ immunoassay method	AT: sRAGE ↑ ($p<0.008$) 1,25D ↔ sRAGE levels ($r=0.61$, $p<0.001$)

			µg/ml) at the end of each hemodialysis session for 8-weeks.		
Human/ Cross-sectional or case control studies	Garg et al./2017[46]	USA	Women with (n=12) or without (n=13) PCOS/ Aged 21-40 years	Follicular fluid / ELISA	sRAGE ↔ 25(OH)D (r=0.65, p=0.0004) In women with PCOS: sRAGE↓ 25(OH)D levels did not differ between the two groups.
	Mayer et al./2018[47]	Czech Republic	500 healthy subjects aged 39.4 ± 14.6 years.	Serum / ELISA	Serum 25(OH)D ≠ sRAGE 95 % of study subjects had normal Vit.D
	Šebeková et al./2015[32]	Germany	276 diabetic subjects (43 T1DM and 233 T2DM) and 121 non-diabetic controls aged 65.0 ± 13.4 years were studied.	Skin and plasma / ELISA	In diabetics, serum 25(OH)D ≠ sRAGE 25(OH)D and sRAGE levels did not differ between diabetics and non-diabetics.
	Sturmer et al./2015[33]	Germany	146 subjects (119 healthy persons and 27 hypertensive patients) aged 57.0 ±15.5 years were studied.	Plasma / ELISA	In whole cohort, Vit.D ≠ sRAGE 25(OH)D and sRAGE levels did not differ between hypertensive and normotensive subjects.
In-vitro	Lee et al./ 2017[38]	Taiwan	Mouse HL-1cardiomyocytes was incubated without and with calcitriol (10 and 100 nM) for 48 h.	Cardiomyocytes/ ELISA	Calcitriol (10 nM): sRAGE ↑ (p<0.01)
	Merhi et al./2018[39]	USA	Human granulosa cells were treated with either media alone (control) or with human glycated albumin without or with vitamin D3 (100 nM) for 24 h.	Follicular fluid /ELISA	sRAGE ↔ 25-OHD (r=0.27, p=0.02)

Animal	Mohammed et al./2019[48]	Egypt	Sham and ovariectomized rats (n=10 in each group) treated with vitamin D3 (500 IU/kg/day/6 weeks, orally).	Serum/ ELISA	There was a significant decrease in serum sRAGE levels in the ovariectomized rats compared to those in the sham group ($p<0.001$). AT: sRAGE ↑
AT, after treatment; PCOS, polycystic ovary syndrome; sRAGE, soluble receptor for advanced glycation end products; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; ↔ represent a positive correlation; ≠ represent no significant correlation Vitamin D treatment increases sRAGE levels in subjects with hypovitaminosis D or pathological conditions.					