Advanced Glycation End Products (AGEs), Receptor for AGEs, Diabetes, and Bone: Review of the Literature

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Diabetes compromises bone cell metabolism and function, resulting in increased risk of fragility fracture. Advanced glycation end products (AGEs) interact with the receptor for AGEs (RAGE) and can make a meaningful contribution to bone cell metabolism and/or alter function. Searches in PubMed using the key words "advanced glycation end-product," "RAGE," "sRAGE," "bone," and "diabetes" were made to explain some of the clinical outcomes of diabetes in bone metabolism through the AGE–RAGE signaling pathway. All published clinical studies were included in tables. The AGE–RAGE signaling pathway participates in diabetic complications, including diabetic osteopathy. Some clinical results in diabetic patients, such as reduced bone density, suppressed bone turnover markers, and bone quality impairment, could be potentially due to AGE–RAGE signaling consequences. However, the AGE–RAGE signaling pathway has some helpful roles in the bone, including an increase in osteogenic function. Soluble RAGE (sRAGE), as a ligand decoy, may increase in either conditions of RAGE production or destruction, and then it cannot always reflect the AGE–RAGE signaling. Recombinant sRAGE can block the AGE–RAGE signaling pathway but is associated with some limitations, such as accessibility to AGEs, an increase in other RAGE ligands, and a long half-life (24 hours), which is associated with losing the beneficial effect of AGE/RAGE. As a result, sRAGE is not a helpful marker to assess activity of the RAGE signaling pathway. The recombinant sRAGE cannot be translated into clinical practice due to its limitations.

Freeform/Key Words: advanced glycation end product, diabetes, osteoporosis, RAGE

Diabetes is a metabolic disease that is associated with increased risk of fracture. Diabetic bone is characterized by changes in bone metabolism, decreased bone mineral content and density, increased fracture rate, and delayed fracture healing. Measuring bone mineral density (BMD) by dual-energy X-ray absorptiometry is the usual method of predicting bone fragility [1]. However, older age, reduced muscle mass or poor balance, duration of type 2 diabetes mellitus (T2DM), complications of DM, poor glycemic control, hypoglycemia, and medications (thiazolidinedione, SGLT2 inhibitors, and insulin) are reported as further compounding the fracture risk of patients with T2DM [1, 2]. The pathophysiology of bone impairment includes compromised bone metabolism (due to oxidant injury, lower IGF-1, higher sclerostin, and lower circulating osteoprogenitor cells), impairment of cell function,

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Abbreviations: ADAM10, a disintegrin and metalloproteinase domain-containing protein 10; AGE, advanced glycation end product; BMD, bone mineral density; BMSC, bone marrow mesenchymal stromal cell; BTM, bone turnover marker; CTX-I, C-telopeptide of type I collagen; DM, diabetes mellitus; esRAGE, endogenous secretory RAGE; HMGB1, high-mobility group box 1; MSC, mesenchymal stem cell; NF-κB, nuclear factor κB; PI3K, phosphatidylinositol 3-kinase; P1NP, *N*-terminal propeptide of type I collagen; RAGE, receptor for AGEs; RANKL, receptor activator for NF-κB ligand; ROS, reactive oxygen species; sRAGE, soluble RAGE; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; TLR, Toll-like receptor.

and extracellular matrix complications (due to the factors such as increased collagen glycation and accumulation of AGEs). Subsequently, diabetes leads to increased rate of bone loss, alteration of bone structure (increased cortical porosity, inhomogeneity, and thinning of cortex), reduced bone turnover, and then a predisposition to bone fragility [1, 2].

Obesity, especially central obesity, as a component of metabolic syndrome has important consequences for morbidity and increases the risk of developing T2DM. Association of fat mass and bone health is bidirectional. The body mass index has a positive correlation with BMD of all sites, as well as anegative correlation with bone turnover markers (BTMs) [1, 3]. However, after assessing femoral neck strength by using the femoral neck composite index, obesity shows negative correlation with femoral neck strength [4]. Additionally, obesity and T2DM have negative effects on bone turnover, trabecular bone volume, and bone microarchitecture, irrespective of diet in rats [5]. Conclusively, the mechanical load resulting from excessive weight along with hyperinsulinemia have positive effects on bone quality. However, hyperglycemia, inflammation, and a change of adipokines in the setting of obesity and insulin resistance have detrimental effects on bone [1].

Generally, the route of obesity, insulin resistance, and T2DM progress in the setting of the integrated metabolic and inflammatory events. Advanced glycation end products (AGEs) and their receptor (RAGE) are considered as important parts of inflammatory events that can cause diabetes and its complications. They are mainly produced due to a high-fat diet or hyperglycemia [6, 7]. Then, it is important to discuss the role of collagen glycation, accumulation of AGEs, and the AGE–RAGE signaling pathway in the changes of bone matrix properties.

In this review, we discuss the alteration of bone health in diabetes, the correlation of the current clinical and paraclinical information with AGE–RAGE interaction, and summarize our current understanding regarding the connection between AGE/RAGE and different signaling pathways that may play a role in bone metabolism. Finally, on the basis of the found reported evidence, we discuss the benefits and limitations of soluble RAGE (sRAGE) as a potential therapeutic intervention.
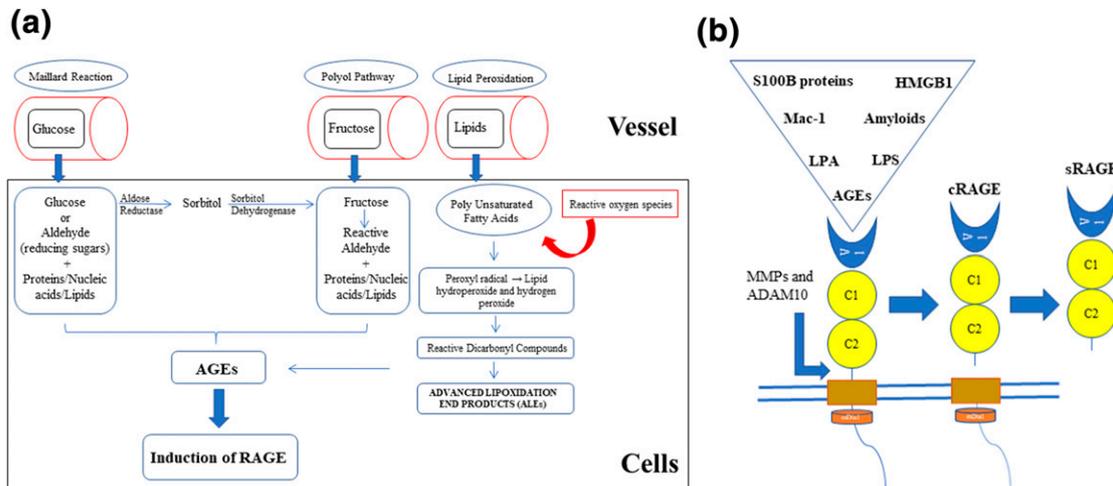
1. AGE/RAGE Production

Hyperglycemia leads to increased production of AGEs, which are the products of nonenzymatic glycation of macromolecules (proteins, lipids, and nucleic acids) with a reducing sugar, known as the Maillard reaction. Excess oxidative stress and a marked rise in reactive oxygen species (ROS) can injure proteins and stimulate their modification. Increased production of oxidized lipids and glucose, in addition to the damaged proteins, can lead to AGE formation. AGEs are generally considered as structurally heterogeneous molecules. The common route of the generation of AGEs in humans with diabetes initially starts with the combination of the carbonyl group of a reducing sugar or aldehyde with lysine and arginine amino acid residues. AGEs can induce an intrinsic signaling pathway inside the cells and promote the development of RAGE on cell membranes. In humans with diabetes, the carboxymethllysine ligands of AGEs are the usual ligands of RAGE. Other than this nonenzymatic reaction of glucose with macromolecules, AGEs can be formed endogenously through the polyol pathway and lipid peroxidation. Furthermore, AGEs can be produced in situations other than hyperglycemia and diabetes [6, 7]. Aging, inflammation, renal failure, increase in intracellular and extracellular stress, oxidative stress, eating high-fat processed foods (rich in saturated fatty acid), heat-treated protein-rich foods (lipids and/or sugar), cigarette smoking, and chronic alcohol consumption can cause production of AGEs [6–10] (Fig. 1a).

Anecdotally, it seems that the same conditions noted to increase AGE/RAGE production have been reported as risk factors for osteoporosis and fracture, including aging, diabetes, inflammation, renal failure, high-fat diet, smoking, and chronic alcohol consumption.

2. RAGE and sRAGE Production

AGEs induce different intrinsic signaling pathways mediated mainly through RAGE. RAGE is a multiligand transmembrane receptor that is structurally similar to immunoglobulin. It is

Figure 1. Formation of AGEs, induction of RAGE (a), and sRAGE production (b). (a) The three different pathways leading to the formation of endogenous AGEs consist of the Maillard reaction, the polyol pathway, and lipid peroxidation. Reducing sugar (glucose, fructose, glyceraldehyde) or reactive dicarbonyl compounds (products of lipid peroxidation) reacts with the macromolecules (such as the amino group of proteins), and then, after the modification process, results in the production of AGEs. Advanced lipoxidation end products (ALEs) are produced by reactive dicarbonyl compounds, which are generated by lipid peroxidation. Polyunsaturated fatty acids (membrane lipids) will produce reactive carbonyl species after being damaged by ROS and further oxidation. Additional modification of ALEs can advance AGE production unless the detoxification becomes dominant. A daily diet including high fat, high sugar, alcohol, and processed foods are important sources of the AGEs. (b) sRAGE production through enzymatic cleavage of external of the RAGE [6, 7, 11]. LPA, lysophosphatidic acid; MMP, matrix metalloproteinase.

composed of an extracellular portion, a transmembrane part, and an intracellular domain. The extracellular domain is constructed by a variable domain (V) and two constant domains (C1 and C2). The variable domain and V-C1 are important for interaction of ligands with RAGE [6, 11] (Fig. 1b).

AGE–RAGE interaction leads to multiple biological effects, including microvascular and macrovascular complications of diabetes (neuropathy, nephropathy, retinopathy, cardiomyopathy, and atherosclerosis). RAGE can be expressed on various cells, including inflammatory cells (monocytes, macrophages, and lymphocytes), endothelial cells, smooth muscle cells, neurons, osteoblasts, and osteoclasts [11, 12]. AGE–RAGE interaction can affect cellular function, motility, and metabolism. AGEs can directly injure cells and tissues through inflammatory and oxidant damages. Additionally, it interacts with variable receptors, especially RAGE, and results in activation of multiple signals, including PKC, phosphatidylinositol 3-kinase (PI3K)/Akt, MAPK/ERK, Src/RhoA, JAK/STAT, and the reduced form of NAD phosphate oxidase. This complex activation of the signals increases the level of nuclear factor κB (NF-κB), Egr-1, or other transcription factors, along with the production of ROS. The results of these events include upregulation of inflammation, induction of oxidative injury, interference with cell motility, and changes in cell metabolism. Additionally, increased cell oxidant stress can further augment AGE production and activate RAGE signaling pathways, leading to altered cell function [11, 13].

Other receptors can interact with AGEs containing AGE–receptor complexes (AGE-R1/OST-48, AGE-R2/80K-H, AGE-R3/galectin-3) and the scavenger receptor family (SR-A, SR-B/CD36, SR-BI, SR-E/LOX-1, FEEL-1, FEEL-2). Scavenger receptors, especially CD36, are thought to participate in endocytosis of AGE proteins. Endocytosed AGEs can be modified by binding to the lysosome and cleared by the kidney [7]. RAGE also has different endogenous and exogenous ligands. It binds endogenous damage-associated proteins, such as AGEs, high-mobility group box 1 (HMGB1), S100/calgranulins, amyloid-β peptide, and other forms of amyloid and macrophage adhesion ligand-1 (MAC-1). Other RAGE ligands include

complement proteins (C3a and C1q), lysophosphatidic acid, phosphatidylserine, lipopoly-saccharide, transthyretin, heparin sulfate, and heat shock proteins [11, 14–16].

sRAGE is a form of the RAGE that can circulate and be measured by ELISA. In humans, two types of sRAGE have been reported. The first form is originated from splicing the external domain of RAGE that contains N-terminal extracellular portion (V-C1-C2 domains). AGEs can induce secretion of matrix metalloproteinases or a disintegrin and metalloproteinase domain-containing protein 10 (ADAM10) that splices RAGE and produces sRAGE (Fig. 1b). Endogenous secretory RAGE (esRAGE) is another form of sRAGE, which is expressed by alternatively spliced precursor mRNA and contains the C-terminal part of RAGE. The main source of sRAGE production is not completely known; however, vascular and immune cells are thought to contribute to the production of sRAGE [17, 18].

sRAGE can bind AGEs without inducing intrinsic signals, due to lacking internal and/or transmembrane parts of the RAGE, leads to potential blocking of AGE–RAGE interaction, and so plays a protective role in the setting of RAGE accumulation [17, 18]. sRAGE has been considered an inhibitor of receptor activator for NF-κB ligand (RANKL)–induced osteo-clastogenesis [19]. Furthermore, an increase in the amount of esRAGE release into bone by applying acidic oligopeptide–tagged esRAGE enhanced esRAGE affinity to hydroxyapatite and improved the therapeutic effects of esRAGE on synovial hyperplasia, cartilage, and bone destruction, in addition to its negative effects on inflammation in rheumatoid arthritis [20].

There is an abundance of published articles that report a correlation between sRAGE and/or esRAGE with different diseases or conditions. However, clinical data around sRAGE are bidirectional. In humans, circulating sRAGE is reduced in the disease conditions such as atherosclerosis, coronary artery disease, hypertension, hypercholesterolemia, chronic ob-structive lung disease, heart failure, and Alzheimer's disease [11, 21]. However, heart failure patients, diabetic and nondiabetic, have higher serum HMGB1 and cleaved RAGE, but lower esRAGE [22]. In terms of correlation of sRAGE with bone parameters, it has been reported that sRAGE had no significant correlation with BMD or fractures in postmenopausal women with T2DM [23], but it had positive link with bone formation [24]. It was also positively correlated with osteopenia and osteoporosis [25], but low esRAGE was reported as a risk factor for vertebral fracture in patients with T2DM [26]. Furthermore, elevated serum levels of sRAGE and reduced esRAGE levels were reported in patients with type 1 DM (T1DM) and T2DM [21]. The bidirectional correlation of sRAGE with different clinical situations can be explained by the fact that excess production of AGEs induces ADAM10 and then breaks down part of the overproduced RAGE, resulting in more sRAGE secretion. Under other circum-stances, alternative splicing of pre-mRNA and/or enzymatic cleavage of RAGE can limit RAGE availability while increasing sRAGE production. Additionally, contribution of the immune system in the production of sRAGE is another factor that may lead to an increase in sRAGE production. Finally, in either situation of AGE/RAGE overproduction or RAGE destruction we might have higher sRAGE levels (Tables 1 and 2) [23–53].

As a result, sRAGE is not a useful marker for assessment of activity of the AGE–RAGE signaling pathway, because it may increase in either excess RAGE production or destruction. However, based on the effects of AGEs on ADAM10, the immune system, and sRAGE production, we may suggest that the sRAGE/AGE ratio is a helpful marker to correlate the activity of the AGE–RAGE signaling pathway with clinical outcomes [28, 54].

3. AGE/RAGE and the Bone Remodeling Process

The bone mass is determined by the balance between osteoblast and osteoclast activity, which is orchestrated by osteocytes in reaction to endocrine and mechanical stimuli. Hematopoietic stem cells differentiate into mononuclear cells and then osteoclasts under the influence of macrophage colony-stimulating factor and RANKL. Bone marrow mesenchymal stem cells (BMSCs) differentiate into osteoblasts, osteocytes, adipocytes, and chondrocytes. Os-teoblasts produce bone matrix proteins, including type I collagen [55, 56]. Osteoblasts are involved in cross talk with osteoclasts through cytokines, the extracellular matrix, and direct

connections; they interact through OPG/RANKL/RANK, RANKL/LGR4/RANK, Ephrin2/ephB4, and Fas/FasL pathways. This interaction between osteoblasts and osteoclasts is important and eventually leads to osteoclast formation, differentiation, or apoptosis. Osteoclasts also participate in bone formation by communicating with osteoblasts via the d2 isoform of the vacuolar (H$^+$) ATPase V0 domain (Atp6v0d2), complement component 3a, semaphorin 4D, or miRNAs [56, 57]. Furthermore, participation of the AGE–RAGE signaling pathway and RAGE ligands (such as HMGB1, S100/calgranulin proteins, and amyloid precursor protein) in bone remodeling [55] and the effects of cytokines such as TGF-β and IGF-1 on the osteoblast's function [57] can explain the outcomes of diabetes and diabetic complications on the determinants of bone strength (including bone mass, composition, microstructure, and material properties).

AGEs (pentosidine, a biomarker for AGEs) can accumulate in human diabetic bone [47]. Evaluation of postmenopausal women with T2DM showed that a lower bone material strength index correlated with the accumulation of AGEs, measured by skin autofluorescence [41]. Generally, AGEs not only induce osteoclastogenesis by upregulation of RANKL mRNA, but they also affect osteoblasts by suppressing cell growth, promoting apoptosis, and downregulating differentiation, which impair mineralization (data from primary human osteoblast culture, human MSCs, and mouse stromal ST2 cells) [58–60]. They can increase [58] or decrease [61] mRNA expression of RAGE in human osteoblasts. However, they increase RAGE mRNA expression in the mouse stromal cell line ST2 (differentiated into osteoblast-like cells) [59]. It was reported that AGEs increase the mRNA expression of RANKL and osterix (transcription factors for osteoblast differentiation) but downregulate alkaline phosphatase and osteocalcin in human osteoblasts [58]. However, they are also reported to increase sclerostin protein but decrease the RANKL expression in osteocyte-like MLO-Y4-A2 cells [62]. They are also shown to reduce Runx2 and osterix protein expression in the mouse stromal cell line ST2 (differentiated into osteoblast-like cells) [59] and decrease not only alkaline phosphatase, but also collagen I mRNA expression, in MSCs [63]. Alternatively, pentosidine was shown to have no effect on human osteoblast expression of osteocalcin, but it does affect human osteoblast function by decreasing alkaline phosphatase and collagen Iα1 [61]. Generally, AGE has biphasic effects on the human fetal osteoblastic cell (hFOB1) survival. Low concentration of AGE in a short period seems to have a protective role by increasing osteogenic function and decreasing osteoclastic function, but the results became reversed with increasing the duration of treatment of hFOB1 by AGE [64]. Accordingly, it has been demonstrated that diabetes increases MSC number initially but later causes reductions in MSCs, leading to trabecular bone loss [65]. In other words, AGEs can increase osterix expression in human osteoblasts [58] and promote osteoblastic growth and cellular alkaline phosphatase activity initially [66], but later induce apoptotic cell death of osteoblasts mainly by interacting with RAGE, activating caspase-3 signaling pathways, increasing production of intracellular ROS, and reducing alkaline phosphatase activity and activation of MAPKs [65, 67–71]. The different attained results of AGEs on osterix, alkaline phosphatase, and RANKL could potentially be due to the timing of assessment of AGEs on cell function and/or the dose of AGEs.

Additionally, by testing ST2 cells and human MSCs, it was shown that AGEs interact with RAGE and increase expression and secretion of TGF-β, which can suppress stromal cell mineralization [60]. The interaction of AGE–RAGE seems to be the dominant way, as their inhibitory effects on Wnt signaling pathway is reversible with the RAGE receptor antagonist FPS-ZM1 [72]. RAGE suppresses cell proliferation through suppression of Wnt, PI3K, and ERK signaling pathways [73]. Concerning bone remodeling, it seems that RAGE signaling pathway participates in the regulation of osteoclast development and activity, but its role in osteoblasts/osteocytes is less studied. It is seems that RANKL stimulates RAGE expression, which is associated with osteoclast differentiation [55, 74], and knocking out RAGE attenuates RANKL-mediated osteoclast differentiation [75]. Consequently, consistent with the effect of RAGE on osteoclast differentiation and activity, RAGE knockout mice showed decreased osteoclast number, reduced bone resorption, increased bone mass, and improved

Table 1.   Studies Reporting Blood/Urine Ages, sRAGE and Bone Changes in Humans in Reverse Order of the Year of Publication Between 2003 and 2018

Author/Journal and Year	Participants	Results	Comments
Choi *et al.*, 2018 [27]	40 (7 men, 33 women) 68–76 y of age (mean age, 70.6 y) 11 vertebral fracture (2 men, 9 women) 29 no fracture (5 men, 24 women)	Serum PEN levels are higher in the vertebral fracture group and positively correlated with FRAX	Serum PEN is a possible biochemical marker for vertebral fractures
Lamb *et al.*, 2018 [24]	3384 men 70–89 y of age	Plasma CML, methylglyoxal, glyoxal, and esRAGE were similar in men with and without DM CML had a positive correlation and esRAGE was inversely associated with FBS esRAGE had a positive correlation with bone formation	Higher blood glucose is positively associated with CML and is reciprocally associated with esRAGE esRAGE can modify or control bone turnover in older men, and CML can predict hip fracture incidence
Tamaki *et al.*, 2018 [28]	1285 men ≥65 y of age	25 fragility fractures The crude fragility fracture HRs (95% CI) for the following are PEN 1.56 (1.05–2.31) esRAGE 0.79 (0.54–1.15) esRAGE/PEN 0.65 (0.44–0.95)	Decreased risk of fragility fractures is noted with higher esRAGE/PEN ratios and this is independent of BMD
Miyazawa *et al.*, 2017 [29]	46 prostate cancer patients receiving antiandrogen treatment 20 received denosumab 26 no denosumab	Decrease in serum PEN and increase in BMD in the denosumab receiver	Denosumab inhibited the rise in PEN levels in patients with prostate cancer antiandrogen therapy
Galliera *et al.*, 2017 [25]	84 postmenopausal women Mean age, 53 ± 6 y	There were 12 subjects with osteoporosis, 32 with osteopenia, and 40 with normal BMD Higher sRAGE was noted in osteopenic and osteoporotic patients	Serum level of sRAGE could potentially be used to monitor osteoporosis progression and fracture risk
Raška *et al.*, 2017 [23]	Postmenopausal women 112 with T2DM 171 control nondiabetics	No association between sRAGE and BMD No association between sRAGE and fracture	No association between RAGE polymorphisms and BMD/ fractures in postmenopausal women with T2DM
Barzilay *et al.*, 2015 [30]	3373 patients Age 78 y (range, 68–102 y) 39.8% men Median follow-up of 9.22 y	Unadjusted HR of hip fracture increased with each 1 SD increase of serum levels of the AGE CML level BMD of the total hip was not correlated with CML levels	Increased levels of CML are associated with risk of hip fracture in and older population independent of hip BMD
Neumann *et al.*, 2014 [31]	128 men and premenopausal women with T1D with and without prevalent fractures	Higher PEN levels in patients with fractures No difference in CML and esRAGE	Increase in AGEs impairs bone quality in T1D

(Continued)

Table 1. Studies Reporting Blood/Urine Ages, sRAGE and Bone Changes in Humans in Reverse Order of the Year of Publication Between 2003 and 2018 (Continued)

Author/Journal and Year	Participants	Results	Comments
Kuroda *et al.*, 2013 [32]	1475 postmenopausal women (66.6 ± 9.0 y)	Urinary PEN and serum homocysteine were associated with vertebral fractures	Severity of vertebral fractures had minor correlation with PEN levels
Tanaka *et al.*, 2011 [33]	765 postmenopausal women	Increase in urinary PEN has a positive correlation and linear relationship with long bone and vertebral fractures	Applying urinary PEN may improve fracture risk classification
Yamamoto *et al.*, 2009 [26]	Japanese T2DM patients: 137 men >50 y of age 140 postmenopausal women with and without VFs	T2DM patients with VFs had a lower esRAGE/PEN ratio. Serum esRAGE and the esRAGE/PEN ratio are correlated with VFs independent of BMD	In T2DM, serum esRAGE and the esRAGE/PEN ratio are better than BMD in assessing VF risk
Schwartz *et al.*, 2009 [34]	928 men and women 70–79 y of age 501 with DM 427 without DM Subjects matched on sex, race, and study site	In the patients with diabetes, PEN was associated with increased clinical fracture incidence and vertebral fracture prevalence	Higher PEN levels may represent decreased bone strength in T2DM, leading to an increase in fracture risk
Pullerits *et al.*, 2009 [35]	88 postmenopausal RA patients received vitamin D$_3$/calcium with or without HRT (estradiol plus norethisterone acetate)	HRT decreased levels of serum sRAGE. Serum sRAGE was correlated with BMD and markers of bone/cartilage metabolism	sRAGE may play a direct or indirect role in bone metabolism
Yamamoto *et al.* 2008 [36]	Japanese T2DM patients: 77 men >50 y of age 76 postmenopausal women	T2DM women with VFs had higher serum PEN levels independent of their BMD; PEN levels are thus associated with VFs in postmenopausal women with T2DM	Serum PEN levels instead of BMD could potentially be a helpful biomarker for assessing the VF risk in postmenopausal women with T2DM; PEN levels may help determine a patient's bone quality
Shiraki *et al.*, 2008 [37]	432 Japanese women Followed for 5.2 ± 3.3 SD	Increased urine PEN levels were associated with vertebral fractures	AGEs are a potential risk factor for vertebral fracture
Hein *et al.*, 2003 [38]	116 osteoporotic patients (34 men and 82 women; mean age, 55 ± 10 y) 44 age-matched healthy controls (18 men and 26 women; mean age, 55 ± 8 y)	Higher PEN and CML serum levels were noted in the group with osteoporosis. Serum PEN was correlated with osteoclast activity/bone resorption	Bone remodeling may be affected by AGE-modified proteins

Abbreviations: CML, N^ε-carboxymethyllysine; FRAX, fracture risk assessment; HR, hazard ratio; HRT, hormone replacement therapy; PEN, pentosidine; P1NP, *N*-terminal propeptide of type I collagen; RA, rheumatoid arthritis; VF, vertebral fracture.

biomechanical strength [76]. Alternatively, with regard to the effects of RAGE on osteoblasts/osteocytes, it is reported that the loss of RAGE decreased femoral cancellous bone accrual, altered architecture, and was associated with reduced expression of alkaline phosphatase, cola1, Runx2, and osterix (osteoblast genes) [12]. Additionally, AGEs have harmful effects on human MSCs [77], and RAGE signaling seems to impair BMSC maintenance under the chronic pathologic conditions, such as diabetes, but not under physiologic conditions [78]. As a result, inhibiting RAGE signaling is a potential approach to improve capacity of BMSCs for differentiation into adipocytes, osteoblasts, and osteocytes in the diabetic condition.

Table 2. Studies Reporting Tissue/Serum AGEs and Bone Changes in Humans in Reverse Order of the Year of Publication Between 2005 and 2018

Author/ Journal and Year	Participants	Results	Comments
Rabelo et al., 2018 [39]	35 postmenopausal women Femoral neck sample 17 fracture (79 ± 2 y) 18 osteoarthritis (66 ± 2 y)	Increase in PEN in femoral neck of osteoporotic fractures independent of age	Increase in PEN contributes to a decrease bone in quality and an increased risk of hip fracture in postmenopausal women
Vaculik et al., 2016 [40]	111 patients hip surgery 70 femoral neck fracture 41 advanced hip osteoarthritis	Both serum and bone PEN levels were increased in patients with hip fractures	PEN can be a potential biomarker to assess bone quality and strength
Furst et al., 2016 [41]	35 postmenopausal women 16 with T2DM 19 matched controls	Increase in AGEs (determined by SAF) was associated with reduced BMSi and lower bone formation marker (P1NP) in T2DM	T2DM: Impaired bone material properties The accumulation of AGEs may lead to lower BMSi
Farlay et al., 2016 [42]	Iliac crest bone biopsies from: 5 fracturing T1DM 5 T1DM with no fracture 5 healthy subjects All age and sex matched	Fracturing T1DM had higher levels of PEN in trabecular bone Positive correlations noted between: HbA1c and PEN HbA1c and bone mineralization	High PEN and bone mineralization could lead to a less flexible and more rigid bone matrix in fracturing T1DM
Karim et al., 2013 [43]	170 human bone samples	More PEN and total AGEs were noted in cancellous bone compared with cortical bone PEN was related to total AGEs in cancellous bone but was weakly correlated in cortical bone	PEN and total AGEs accumulate differently in cancellous and cortical bone. Quantifying total AGEs and PEN is important for a complete understanding of the AGEs in bone
Karim et al., 2012 [44]	42 cancellous bone obtain from 24 men 18 women Age 18 to 97 y (mean, 59.3 ± 22.1 y)	More trabecular rods than plates and more microdamage were noted in highly glycated samples High levels of AGEs decrease bone mechanical measures against fracture (yield strain, ultimate strain, and toughness)	AGEs can heterogeneously modify cancellous bone trabecular microarchitecture, which can affect bone fragility
Momma et al., 2012 [45]	193 Japanese men Median age, 43 y (range, 37.0–55.0 y)	Negative correlation between SAF and osteo sono assessment index	AGE accumulation can potentially affect bone strength
Dong et al., 2011 [46]	18 cortical bone from cadaveric femur of men 6 young (31 ± 6 y old) 6 middle-aged (51 ± 3 y old) 6 elderly (76 ± 4 y old)	The concentration of AGEs depends on age of donor and biological tissue ages AGEs concentration has a positive correlation with osteoclast activities	AGEs accumulation in human cortical bone can potentially affect bone remodeling

(Continued)

Table 2. Studies Reporting Tissue/Serum AGEs and Bone Changes in Humans in Reverse Order of the Year of Publication Between 2005 and 2018 (Continued)

Author/ Journal and Year	Participants	Results	Comments
Oren *et al.*, 2011 [47]	20 total knee arthroplasty	Higher PEN levels in tissue of patients with diabetes	The inverse relationship between synovial fluid osteocalcin levels and the levels of AGEs in the joint may indicate that AGEs can affect bone healing in individuals with diabetes
	10 with diabetes, 10 controls	Negative correlation between osteocalcin and HP in cartilage	
	Synovial fluid markers and collagen crosslinks in bone and cartilage were assessed	Negative correlation between osteocalcin and PEN in cartilage of patients with diabetes	
Tang *et al.*, 2007 [48]	8 fresh human cadaver femoral heads were paired for ribosylation and control treatments	AGEs content increased with age in control group AGEs in cancellous bone cores have correlation with damage in treated group	AGEs can increase the tendency of cancellous bone to fracture
Viguet-Carrin *et al.*, 2006 [49]	19 L3 vertebrae after necropsy; age 26–93 y; 10 men, 9 women	BMD and trabecular PEN were correlated with failure load and work to fracture	PEN has a negative impact on vertebral mechanical properties
			Posttranslational modification of type 1 collagen can affect skeletal fragility
Hein *et al.*, 2006 [50]	8 patients with osteoporosis	AGEs imidazolone and CML were found in osteoporotic bone specimens (iliac crest)	There is an inverse correlation between the AGEs and the number of osteoblasts on the surface of a trabecular bone
	Iliac crest bone biopsy	Advanced age was associated with the higher intensity of AGEs	AGEs modify bone proteins and may impair bone remodeling
Saito *et al.*, 2006 [51]	16 women (78 ± 6 y of age) with intracapsular hip fracture	High-mineralized bone had a higher PEN content than did low-mineralized	Poor bone quality in osteoporosis could be due to reduction in bone mineralization, lower enzymatic cross-links, and excessive PEN formation
	16 age- and sex-matched postmortem controls (76 ± 6 y of age)	Low-mineralized bone with fracture had higher PEN content than did control	
Hernandez *et al.*, 2005 [52]	32 thoracic vertebral bodies from cadavers (16 men and 16 women; 54–94 y of age)	PEN was correlated with structural ductility	Ductility of trabeculae is weakly affected by nonenzymatic glycation
Odetti *et al.*, 2005 [53]	104 nondiabetic subjects (74 women and 30 men), 72 ± 1 y of age	Samples of human leg bone (femur or knee) Advanced age was associated with increase in PEN concentration in cortical bone	PEN could potentially be used as a biomarker for bone density loss

Abbreviations: BMSi, bone material strength index; CML, N^{ε}-carboxymethyllysine; HP, hydroxylysylpyridinoline; PEN, pentosidine; P1NP, *N*-terminal propeptide of type I collagen; SAF, skin autofluorescence.

Importantly, note that high glucose levels have synergistic effects with AGEs in impairing the mineralization process [79], but RAGE knockout did not affect bone metabolism in the diabetic condition. The reduction of osteoclast formation due to RAGE deletion was reported only under physiological, but not the diabetic, condition [80], which may indicate a partial protective role of RAGE in diabetes or highlight the roles of other pathophysiologic mechanisms in bone metabolism of the diabetic condition.

Furthermore, we should not underestimate the roles of other RAGE ligands, other than AGEs, in the pathophysiology of diabetic osteopathy. Myeloid cells, osteoblasts, and osteoclasts can secrete HMGB1. HMGB1, which is a ligand for RAGE and Toll-like receptor (TLR)2

and TLR4, works similar to a chemotactic agent for osteoblasts and osteoclasts during the bone remodeling process. Apoptotic bone cells release HMGB1 into the bone marrow and increase levels of RANKL, TNFα, and IL-6 in osteoblasts and stromal cells. Additionally, HMGB1 plays an important role in inflammatory reactions and the bone remodeling process, especially bone resorption [81].

HMGB1 activates PI3K, Akt, and AP-1 pathways and increases integrin ($\alpha_5\beta_1$ integrin) expression through the RAGE/PI3K/Akt/c-Jun/AP-1–dependent pathway [82]. HMGB1, S100, and amyloid precursor protein (APP) are the RAGE ligands that increase osteoclast differentiation through RANKL [19, 74, 75]. S100A8 and S100A9 are initiators and promoters of the inflammatory response. N-glycans, RAGE, and TLR4 are known receptors of S100A8. However, S100A8, but not S100A9, is able to stimulate osteoclast differentiation and increase osteoclast number. Additionally, it was reported that S100A8-mediated bone resorption happens through TLR4, given evidence that S100A8-mediated osteoclast stimulation cannot be blocked by either using RAGE-blocking antibody or sRAGE [83], but we should consider that sRAGE can bind AGEs and block AGE–RAGE interaction, which technically has no effects of S100A8/RAGE interaction. Furthermore, S100A7 can interact with RAGE and increase activity of matrix metalloproteinases of osteosarcoma cells, promoting migration and invasion of these cells [84].
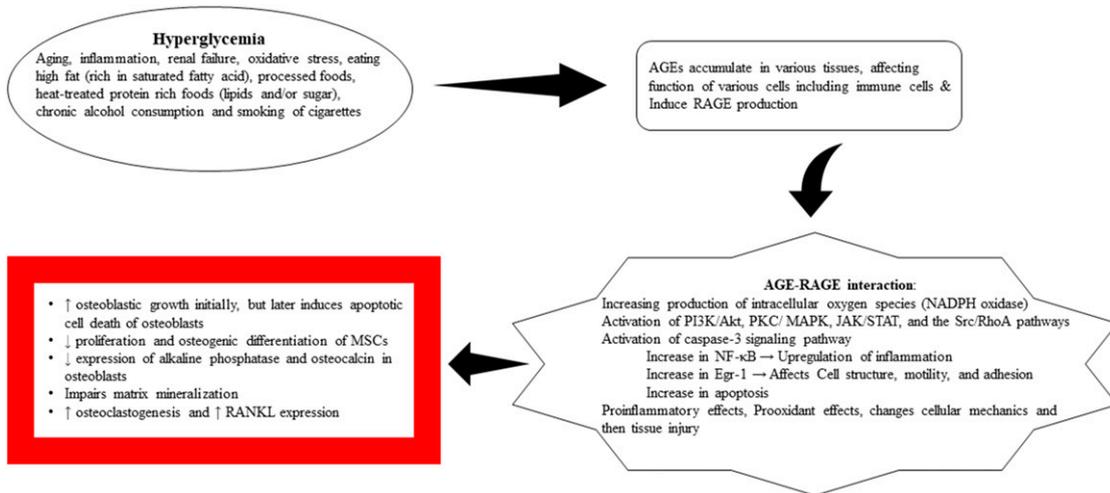
Generally, RAGE has an important role in diabetic complications, including diabetic osteopathy. As mentioned earlier, it interacts with different ligands such as AGEs, HMGB1, S100 proteins, β-amyloids, β_2-integrin Mac-1, and pyridinoline (a collagen crosslink) and then activates NF-κB and Erg1, which are involved in inflammation, activation of innate immune system, cell survival signaling, tissue regeneration, and immune modulation [11, 55, 85–87] (Fig. 1b).

However, AGE–RAGE signaling pathway seems to have some protective roles in the skeletal system. It is necessary for the skeleton's response to anabolic effects of PTH. Absence of RAGE weakened PTH-mediated increases in femoral cancellous bone formation and trabecular number but had no effects on the response of vertebral cancellous bone to PTH [12]. Additionally, during development of the skeleton and endochondral ossification, PTH/PTH-related peptide receptor and Indian hedgehog (Ihh) participate in proliferation and maturation of chondrocytes. AGEs have negative effects on tissue repair capacity and reduce cartilage matrix production and chondrocyte differentiation through a Rho family GTPase mechanism. AGEs downregulate Ihh and Col10a1, but upregulate PTH-related peptide receptor [88] (Fig. 2).

4. AGE/RAGE, Bone Matrix, and BTMs

Bone turnover includes resorption of damaged bone by osteoclasts and replacing new bone by osteoblasts. BTMs generally consist of bone proteins (the products of collagen degradation/production) or enzymes that are presumed to reflect the rate of bone formation and resorption. Increased osteoclast activity leads to the resorption and the release of bone soft tissue constituents into serum and urine. C-telopeptide of type I collagen (CTX-I) is the product of collagen degradation that shows osteoclast activity. Osteoblasts secrete collagen and other molecules that participate in osteoid formation. N-terminal propeptide of type I collagen (P1NP) is a bone protein that reflects osteoblast activity and function [89]. Measuring the concentration of BTMs in blood and urine helps to assess the process of resorption and formation. P1NP and CTX-I are recommended by the International Osteoporosis Foundation and the International Federation of Clinical Chemistry to assess fracture risk and response to treatment in patients with osteoporosis [89, 90]. Diabetes, obesity (visceral obesity), and insulin resistance are associated with lower BTM levels (P1NP and CTX-I) [1, 91], which are the result of AGE–RAGE interactions and reduced bone formation in the diabetic condition, but is opposite to the fact that diabetes increases osteoclast activity.

Posttranslational modification of collagen is crucial for collagen stability and plays an important role in bone biology and strength. The collagen crosslinking is not only important

Hyperglycemia
Aging, inflammation, renal failure, oxidative stress, eating high fat (rich in saturated fatty acid), processed foods, heat-treated protein rich foods (lipids and/or sugar), chronic alcohol consumption and smoking of cigarettes

AGEs accumulate in various tissues, affecting function of various cells including immune cells & Induce RAGE production

AGE-RAGE interaction:
Increasing production of intracellular oxygen species (NADPH oxidase)
Activation of PI3K/Akt, PKC/ MAPK, JAK/STAT, and the Src/RhoA pathways
Activation of caspase-3 signaling pathway
    Increase in NF-κB → Upregulation of inflammation
    Increase in Egr-1 → Affects Cell structure, motility, and adhesion
    Increase in apoptosis
Proinflammatory effects, Prooxidant effects, changes cellular mechanics and then tissue injury

- ↑ osteoblastic growth initially, but later induces apoptotic cell death of osteoblasts
- ↓ proliferation and osteogenic differentiation of MSCs
- ↓ expression of alkaline phosphatase and osteocalcin in osteoblasts
- Impairs matrix mineralization
- ↑ osteoclastogenesis and ↑ RANKL expression

Figure 2. The process of development and function of AGE–RAGE signaling [6, 7, 11, 12, 56, 59–64, 79].

for bone quality, but it also participates in remodeling process by affecting the differentiation of bone cells and regulation of their behavior [92]. The collagen crosslinks include lysyl oxidase–mediated enzymatic and glycation-induced nonenzymatic crosslinks. The lysyl oxidase–mediated enzymatic crosslink stabilizes the collagen fibers and makes them stronger. However, the nonenzymatic crosslinks, produced by the reaction of reducing sugar with protein (AGEs), is associated with decreased bone strength. Collagen of diabetic bone contains fewer enzymatic crosslinks, which can affect bone strength without a reduced BMD [93]. Importantly, note that osteoblast interaction with collagen leads to an increase in lysyl oxidase expression, but glycated collagen cannot increase lysyl oxidase production. Integrins and discoidin domain receptors are two main binding sites for collagen on osteoblasts. Glycation of collagen can diminish binding capacity of collagen with osteoblasts through discoidin domain receptor 2 (DDR2) and integrin receptors [94, 95], which probably leads to less lysyl oxidase production. However, AGEs can potentially increase collagen production, but with enhancing degradation they lead to less collagen [96]. Alternatively, AGE-modified proteins, such as AGE-modified β_2-microglobulin, decreased collagen synthesis in fibroblasts through interaction with RAGE. Additionally, they have proinflammatory effects that enhance collagenase [97]. Lastly, modification of collagen through the glycation processes changes the charge profile of collagen (eliminates the positive charge of lysine) and affects the mass and architecture of fibers, which end up having less solubility and flexibility, but more toughness to degradation by proteases [18]. As a result, resistance to degradation of glycated collagen could be the reason for lower CTX-I levels in patients with DM, despite that diabetes increases osteoclast activity. Additionally, reduction of osteoblast activity and lowered collagen production lead to a lower P1NP concentration in patients with diabetes (Fig. 2).

5. Current Treatments and Limitations of sRAGE

Growing efforts have been made to find an effective solution that can inhibit or reduce the detrimental effects of AGE–RAGE interaction. Current reported therapeutic interventions against the AGE–RAGE signaling pathway include treatments targeting AGEs, RAGE, postreceptor signaling pathways, or the complications of AGE–RAGE interactions. The list of reported therapeutic interventions for AGE- and RAGE-associated pathology includes: AGE inhibitor (aminoguanidine), AGE crosslink breaker (alagebrium and related compounds), antioxidants, medications, and natural substances with anti-AGE/RAGE properties, such as

bisphosphonates, statin, metformin, angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonist, pyridoxamine, ascorbic acid, *N*-acetylcysteine, and vitamins D and K [14, 98].

Additionally, the effects of antidiabetic medications on RAGE expression and bone health could be different. There are antidiabetic medications, such as metformin [99, 100] and glucagon-like peptide-1 (GLP-1) agonist [101, 102], that have negative effects on the AGE–RAGE signaling pathway and some beneficial effects on BMD and/or fracture [1]. However, thiazolidinediones [peroxisome proliferator-activated receptor-γ (PPAR-γ) agonist] induce adipogenesis and osteoclastogenesis that lead to increases in fracture rate [1], but the nuclear receptor PPAR-γ activation can inhibit RAGE expression [103].

Targeting RAGE is a potential approach to prevent diabetic complications. Mainly animal experiments have shown some benefits of different products to target RAGE, including (Fig. 3):

1. sRAGE as a ligand decoy [11]
2. Anti-RAGE antibody [11]
3. Small-molecule RAGE antagonists [11]
4. Longistatin, which blocks RAGE stimulation by binding to the RAGE V domain [104]
5. Aptamers (RAGE aptamers) [11]
6. Inhibitors of the cytoplasmic domain of RAGE (ctRAGE) include 13 small molecules [105]
7. Genetic suppression of RAGE by using RAGE siRNA (siRAGE) [106]

Despite the impressive improvement in the landscape of our understanding regarding the AGE–RAGE signaling pathway and the presence of variable therapeutic interventions, no clinically successful human study was found to be able to block the pathway efficiently and probably alleviate diabetes-related complications. However, putting different pieces of this amazing puzzle together in a goal-oriented fashion may give us insight into the limitations of the therapeutic approaches fighting against the AGE–RAGE signaling pathway.

Among all of the reported therapeutic options to alleviate activity of the AGE–RAGE signaling pathway, recombinant sRAGE, as a ligand decoy, was thought to be the most effective method. sRAGE can inhibit RANKL-induced osteoclastogenesis [19], reduce inflammatory stresses [107], and protect against weight gain and insulin resistance in high-fat diet–fed mice, but it can increase the levels of other RAGE ligands, such as Hmgb1 mRNA [108]. Furthermore, the important part of RAGE for interaction with RAGE ligands is the variable domain [6, 11], which is AGE specific, and AGEs are generally complex and heterogenic compounds [7]. As a result, recombinant sRAGE, with a fixed variable domain, can partially block the produced AGEs.

RAGE and RAGE ligands, such as amyloid-β, AGEs, and HMGB1 lipopolysaccharide, play a crucial role in engaging macrophages [6, 14, 109], but AGEs increase lipid accumulation in macrophages, which can potentially disable macrophages [110]. Alternatively, activated macrophages have an important role in the accumulation of AGE-albumin in tissues as a defense mechanism [14]. Then, we can suspect that sRAGE can block the AGEs and improve macrophage defensive role, but it is also reported that sRAGE reduces macrophage phagocytosis, perhaps by opposing RAGE-mediated and other phosphatidylserine receptor–mediated phagocytosis [111].

Moreover, the accessibility of sRAGE to the AGEs seems to be important, as transfecting BMSCs [107] or umbilical cord–derived MSCs [112] by sRAGE leads to better suppressive effects on inflammation [107] and improved protection against RAGE-induced neuronal cell death [112].

The last thing about RAGE is its possible protective role alongside AGEs. Obesity has positive correlations with both fat and lean mass in humans, which means that an increase in body weight is naturally associated with an increase in lean and fat mass. However, knocking out RAGE leads not only to significantly lower insulin resistance and fat mass, but also to reduced lean mass in high-fat diet–fed mice [108]. Additionally, in terms of bone
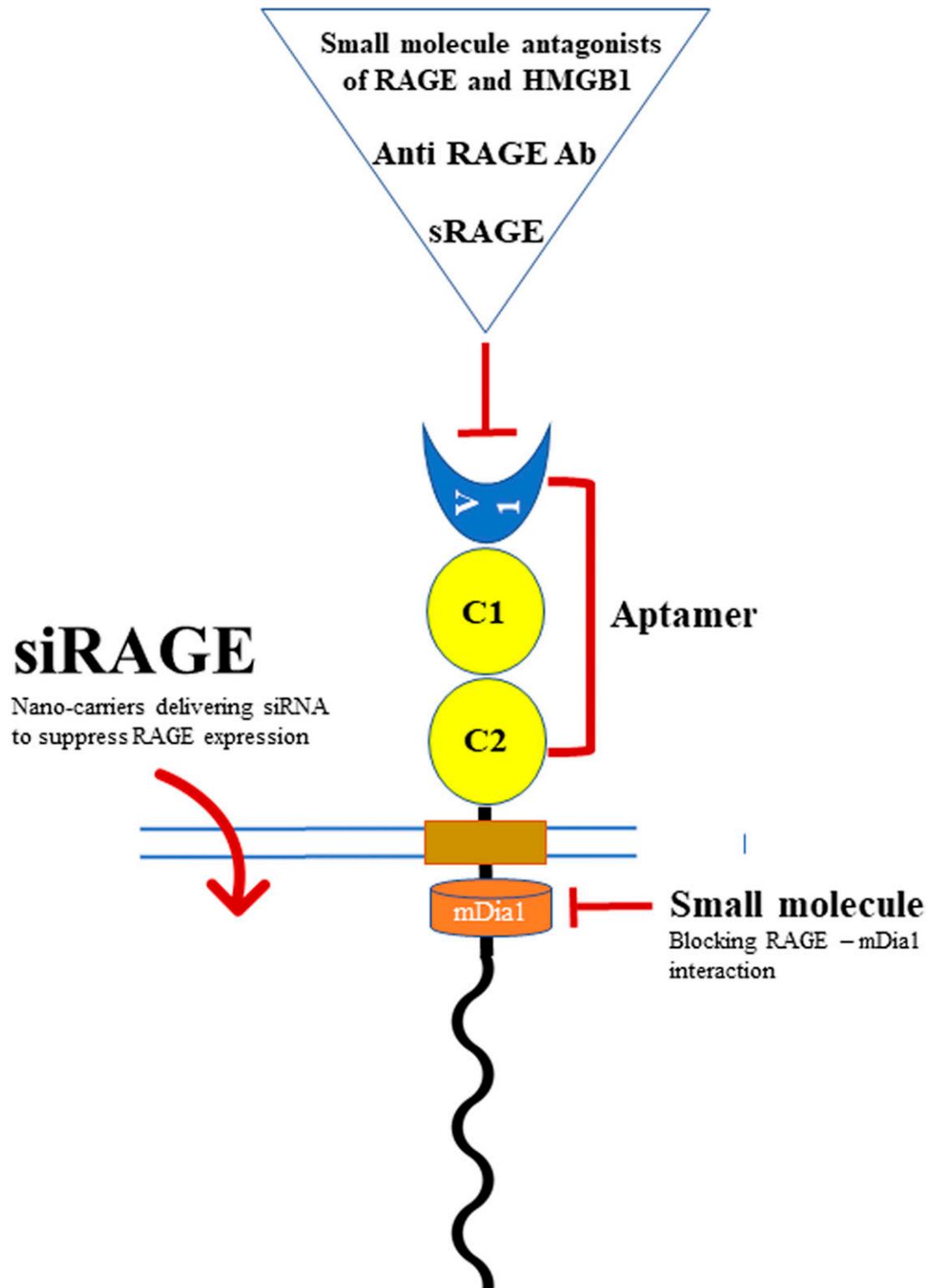
Figure 3. Diverse strategies to target RAGE function and expression.

pathophysiology, AGEs initially increase osteoblastic osterix expression [58] and promote osteoblastic growth [68], and their receptor (RAGE) improves the skeleton's response to anabolic effects of PTH [12]. As a result, blocking the AGE–RAGE interaction by recombinant sRAGE that has a >24-hour elimination half-life [113] not only has limitations, such as

heterogeneity of AGEs, accessibility of sRAGE, and an increase in the levels of other RAGE ligands, but it also can lead to loss of the beneficial effects of AGE–RAGE signaling.

6. Conclusion

AGEs are heterogeneous molecules that mainly result from the nonenzymatic reaction of a sugar with macromolecules. AGEs induce intrinsic cellular signaling that leads to the development of RAGE. The AGE/RAGE production and osteoporosis share common risk factors. AGE–RAGE interaction could be a potential reason for suppression of BTMs (P1NP and CTX) in the setting of diabetes. sRAGE may be elevated in either excess RAGE production or destruction, and it does not always reflect AGE–RAGE signaling activities. sRAGE is a beneficial option for alleviating the effects of the AGE–RAGE signaling pathway in bone, but because of the limitations it cannot be translated into clinical practice.

Acknowledgments

Additional Information

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