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.
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 anagative 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 carboxymethyllysine 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
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 \( \kappa B \) (NF-\( \kappa B \)), 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-\( \beta \) peptide, and other forms of amyloid and macrophage adhesion ligand-1 (MAC-1). Other RAGE ligands include

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**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) react 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. Polynsaturated 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, lysophosphatic acid; MMP, matrix metalloproteinase.
complement proteins (C3a and C1q), lysophosphatidic acid, phosphatidylserine, lipopolysaccharide, 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 osteoclastogenesis [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 obstructive 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 circumstances, 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. Osteoblasts 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 isoformal 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 osteoclasts 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
| Author/Journal and Year | Participants | Results | Comments |
|-------------------------|--------------|---------|----------|
| Choi et al., 2018 [27]  | 40 (7 men, 33 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 |
|                         | 68–76 y of age (mean age, 70.6 y) | | |
|                         | 11 vertebral fracture (2 men, 9 women) | | |
|                         | 29 no fracture (5 men, 24 women) | | |
| Lamb et al., 2018 [24] | 3384 men | Plasma CML, methylglyoxal, glyoxal, and esRAGE were similar in men with and without DM | Higher blood glucose is positively associated with CML and is reciprocally associated with esRAGE |
|                         | 70–89 y of age | CML had a positive correlation and esRAGE was inversely associated with FBS | esRAGE can modify or control bone turnover in older men, and CML can predict hip fracture incidence |
| Tamaki et al., 2018 [28] | 1285 men | Decreased risk of fragility fractures is noted with higher esRAGE/PEN ratios and this is independent of BMD | |
|                         | 65 y of age | 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) | |
| Miyazawa et al., 2017 [29] | 46 prostate cancer patients receiving antiandrogen treatment | 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 |
|                         | 20 received denosumab | | |
|                         | 26 no denosumab | | |
| Galliera et al., 2017 [25] | 84 postmenopausal women | There were 12 subjects with osteoporosis, 32 with osteopenia, and 40 with normal BMD | Serum level of sRAGE could potentially be used to monitor osteoporosis progression and fracture risk |
|                         | Mean age, 53 ± 6 y | Higher sRAGE was noted in osteopenic and osteoporotic patients | |
| Raška et al., 2017 [23] | Postmenopausal women | No association between sRAGE and BMD | No association between RAGE polymorphisms and BMD/fractures in postmenopausal women with T2DM |
|                         | 112 with T2DM | No association between sRAGE and fracture | |
|                         | 171 control nondiabetics | | |
| Barzilay et al., 2015 [30] | 3373 patients | Unadjusted HR of hip fracture increased with each 1 SD increase of serum levels of the AGE CML level | Increased levels of CML are associated with risk of hip fracture in and older population independent of hip BMD |
|                         | Age 78 y (range, 68–102 y) | BMD of the total hip was not correlated with CML levels | |
|                         | 39.8% men | | |
|                         | Median follow-up of 9.22 y | | |
| 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)
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.
| Author/Journal and Year | Participants | Results | Comments |
|-------------------------|--------------|---------|----------|
| Rabelo et al., 2018 [39] | 35 postmenopausal women<br>Femoral neck sample<br>17 fracture (79 ± 2 y)<br>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<br>70 femoral neck fracture<br>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<br>16 with T2DM<br>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<br>The accumulation of AGEs may lead to lower BMSi |
| Farlay et al., 2016 [42] | Iliac crest bone biopsies from: Fracturing T1DM<br>5 fracturing T1DM<br>5 T1DM with no fracture<br>5 healthy subjects | Fracturing T1DM had higher levels of PEN in trabecular bone<br>Positive correlations noted between: HbA1c and PEN<br>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<br>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<br>24 men<br>18 women<br>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<br>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<br>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<br>6 young (31 ± 6 y old)<br>6 middle-aged (51 ± 3 y old)<br>6 elderly (76 ± 4 y old) | The concentration of AGEs depends on age of donor and biological tissue ages<br>AGEs concentration has a positive correlation with osteoclast activities | AGEs accumulation in human cortical bone can potentially affect bone remodeling |
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 that AGEs can affect bone healing in individuals with diabetes.

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

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 10 with diabetes, 10 controls Synovial fluid markers and collagen crosslinks in bone and cartilage were assessed | Higher PEN levels in tissue of patients with diabetes Negative correlation between osteocalcin and HP in cartilage Negative correlation between osteocalcin and PEN in cartilage 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 |
| 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 Iliac crest bone biopsy | AGEs imidazolone and CML were found in osteoporotic bone specimens (iliac crest) Advanced age was associated with the higher intensity of AGEs | There is an inverse correlation between the AGEs and the number of osteoblasts on the surface of a trabecular bone 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 16 age- and sex-matched postmortem controls (76 ± 6 y of age) | PEN was correlated with structural ductility | Poor bone quality in osteoporosis could be due to reduction in bone mineralization, lower enzymatic cross-links, and excessive PEN formation Ductility of trabeculae is weakly affected by nonenzymatic glycation |
| 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 | PEN could potentially be used as a biomarker for bone density loss |
| 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 | |

Abbreviations: BMSi, bone material strength index; CML, N-carboxymethyllysine; HP, hydroxylysylpyridinoline; PEN, pentosidine; P1NP, N-terminal propeptide of type I collagen; SAF, skin autofluorescence.
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 (α5β1 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, β2-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
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 β2-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-\( \gamma \) (PPAR-\( \gamma \)) agonist] induce adipogenesis and osteoclastogenesis that lead to increases in fracture rate [1], but the nuclear receptor PPAR-\( \gamma \) 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 heterogeneous 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-\( \beta \), 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
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

Figure 3. Diverse strategies to target RAGE function and expression.
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.

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