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Review

Advanced glycation end products (AGEs) and its receptor, RAGE, modulate age-dependent COVID-19 morbidity and mortality. A review and hypothesis

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ABSTRACT

Coronavirus Disease 2019 (COVID-19), caused by the novel virus SARS-CoV-2, is often more severe in older adults. Besides age, other underlying conditions such as obesity, diabetes, high blood pressure, and malignancies, which are also associated with aging, have been considered risk factors for COVID-19 mortality. A rapidly expanding body of evidence has brought up various scenarios for these observations and hyperinflammatory reactions associated with COVID-19 pathogenesis. Advanced glycation end products (AGEs) generated upon glycation of proteins, DNA, or lipids play a crucial role in the pathogenesis of age-related diseases and all of the above-mentioned COVID-19 risk factors. Interestingly, the receptor for AGEs (RAGE) is mainly expressed by type 2 epithelial cells in the alveolar sac, which has a critical role in SARS-CoV-2-associated hyper inflammation and lung injury. Here we discuss our hypothesis that AGEs, through their interaction with RAGE amongst other molecules, modulates COVID-19 pathogenesis and related comorbidities, especially in the elderly.

1. Introduction

Coronavirus Disease 2019 (COVID-19) is a novel communicable disease caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), with remarkably heterogeneous and protean manifestations, from asymptomatic to life-threatening severe pneumonia. In some patients, especially the elderly, COVID-19 infection causes acute respiratory distress syndrome (ARDS), multiorgan failure, and death[1-3]. Various predisposing factors and comorbidities, such as aging, sex, ethnicity, obesity, diabetes, high blood pressure, malignancies, kidney and liver disorders, have been identified as COVID-19 risk factors of mortality [4]. Among these variables, age confers a substantial risk to COVID-19 mortality. A recent cohort study with a large sample volume showed that aging was substantially associated with increased death risk among people aged 80 by 20-fold compared to 50–59-year-old age group people [5]. Cardiovascular disease, metabolic disorders, malignancies, neurodegeneration, and autoimmune diseases, and age-related inflammatory conditions or inflammaging are among age-associated medical conditions that can enhance morbidity and mortality of COVID-19 infection (Fig. 1) [6,7]. Finding aging-related mechanisms that underpin COVID-19 fatality and putting in place preemptive measures potentially may help to mitigate the overwhelming effects of the COVID-19 pandemic on health care systems. COVID-19, in essence, is a hyperinflammatory reaction, considering that the cytokine storm plays a substantial role in its pathogenesis, any pre-existing inflammatory condition, including inflammaging, may exacerbate COVID-19- associated morbidity and mortality [8,9].

Nevertheless, the exact mechanism of inflammaging and its potential adverse effects on health outcomes remain unrecognized [7]. Advanced glycation end products (AGEs), a highly heterogeneous group of compounds produced by glycation of amino acids, lipids, and DNA molecules, have been shown to contribute to the age-associated increase in inflammation or "inflammaging"[10]. Both aging and hyperglycemia accelerate the formation of AGEs, which serve as ligands to several cellular receptors, including the receptor for advanced glycation end-products (RAGE), which is expressed mainly by the alveolar epithelial

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cells and macrophages, that have a central role in the lung inflammation caused by COVID-19 [11-14]. Furthermore, increased levels of AGEs are associated with conditions, including diabetes, obesity, and cardiovascular disease, which increase COVID-19 related morbidity and mortality [15]. Thus, we hypothesize that AGEs may contribute to several aspects of COVID-19 pathogenesis in the elderly. Considering the importance of the RAGE pathway as a novel therapeutic target for COVID-19 management [14,16,17] here, for the first time, we reviewed the RAGE receptor with an emphasis on its ubiquitous ligands, AGEs, and its probable association with severe COVID-19 risk factors, including aging, hypertension, obesity, and hyperglycemia (Fig. 1), in the following, we propose potential treatments interfere with AGE-RAGE interaction.

2. Ages formation and contribution to inflammation and oxidative stress through RAGE signaling

AGEs are the principal product of the sequential non-enzymatic glycation of protein by sugars such as glucose and fructose [18]. The production of AGEs is primarily driven by the metabolism of glucose and fructose and, to a lesser extent by threonine and lipid peroxidation. These reactions result in the generation of highly reactive alpha dicarbonyl groups, which propagate the generation of AGEs [10]. Methylglyoxal (MGO) is potentially the most crucial propagator molecule for AGEs generation, primarily produced as a byproduct in glycolysis during the conversion of dihydroxyacetone phosphate to glyceraldehyde-3 phosphate [19]. The AGEs are created through the alteration of lipids, nucleotides, or amino acids (lysine or arginine) by propagators such as MGO [10].

The RAGE is a single receptor for multiple ligands first identified and isolated from the bovine lung [20]. RAGE belongs to the heterogeneous group of pattern recognition receptors (PRRs) that can recognize a typical pattern within diverse ligands, including S100 proteins with calcium-binding properties and cytokine-like functions, High mobility group box-1 protein (HMGB1), β2-Integrin, Macrophage 1 antigen (Mac-1), or CD11b and various other ligands [21]. RAGE has three immunoglobulin-like domains, with the transmembrane and cytoplasmic domains. The two other forms of RAGE: dominant-negative RAGE (DN-RAGE) and endogenous secretory RAGE (esRAGE), are alternative splicing products. The DN-RAGE lacks the cytoplasmic domain, and both the cytoplasmic and transmembrane domain is absent in esRAGE [21].

Several signaling pathways contribute to AGEs-RAGE interactions. The actin-binding molecule, mDia1 (diaphanous1), serves as an adaptor molecule for RAGE signaling in the various cell types [22]. The activation of the RAGE signaling pathway through phosphatidylinositol-3 kinase (PI-3 K), Ki-Ras, and the mitogen-activated protein kinase (MAPKs), Erk1, and Erk2 lead to nuclear factor-kB (NF-kB) activation and range of inflammatory response, which is mediated by cytokine such as IL-6 [21,22]. RAGE also induces a spectrum of pathological effects through the activation of oxidative stress by activation of Rac, and subsequently, nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, an enzyme that has a critical function in the production of the free radical superoxide[22].

3. The association of AGEs and risk factors for COVID-19 death

3.1. 3.1Aging

The clinical and epidemiological reports of COVID-19 reveals that age and different comorbidities raise the risk of infection with more critical lung involvement and death[5,23]. COVID-19 has highlighted the susceptibility of the elderly to emerging infectious diseases[6]. The study of 5700 patients in New York City revealed the importance of aging in the COVID-19-related mortality in people older than 80 years old compared to all other age groups [24]. Similarly, the study in the UK showed that more than 90% of the COVID-19-related deaths were in people over 60[5]. The accumulation of AGEs during aging is associated with an enhanced risk of developing various chronic diseases that disproportionally afflict older individuals[18]. AGEs accumulate gradually with age in adults aged 65 and older, and their levels correlate with an

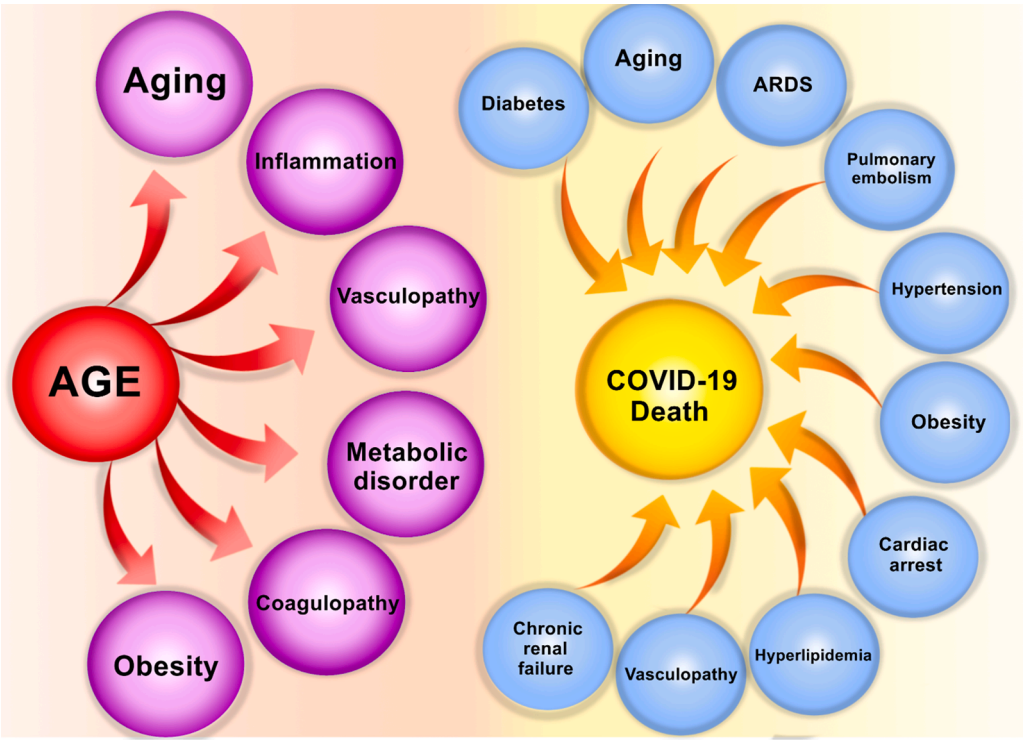

Fig 1. The schematic illustration between AGEs and COVID-19 risk factors. All of the disorders related to AGE/RAGE pathway could be as COVID-19 associated morbidity and mortality.

increased risk of mortality due to all-cause or cardiovascular disease (CVD) [25,26]. We and others have recently reviewed the evidence for the accumulation of AGEs with age and its relevance to aging and age-related diseases, including diabetes [22,27]. The AGEs may potentially trigger COVID-19 severity and mortality through their classic receptor RAGE, which is mainly expressed on the surface of type one and type two alveolar epithelial cells as well as alveolar macrophages, the cells that have indispensable roles in COVID-19-related acute lung injury [28,29].

3.2. Hypertension

Hypertension is the most prevalent comorbidity reported in hospitalized COVID-19 patients, with an association with higher risks of adverse outcomes, including mortality, ICU admission, and heart failure [30]. Hypertension is considered a remarkable all-cause mortality risk in COVID-19 patients[31]. The Renin-angiotensin system (RAS) has a critical role in controlling blood pressure[32]. The angiotensin-converting enzyme-2 (ACE2), which serves as the receptor for SARS-CoV-2, exert a pivotal role in this complex system and virtually has a crucial impact on susceptibility to the severe form of COVID-19[33]. ACE2, a homologue of angiotensin-converting enzyme (ACE), was primarily described by Donoghue et al. in 2000[34]. The ACE2 is a type 1 integral membrane glycoprotein composed of 805 amino acids, and its gene is located on the short arm of the X chromosome (Xp22)[34]. It is constitutively expressed by the epithelial cells of the lungs, kidney, intestine, and blood vessels[35]. ACE2 has several critical roles, including regulation of blood pressure, cardiac function, and it serves as the principal receptor for three viruses in the coronaviridae family with clinical relevance, including HCoV-NL63, SARS-CoV, and SARS-CoV-2 [36,37]. Several lines of evidence show close interaction between AGE-RAGE and RAS systems, which may be mediated by reactive- oxygen (ROS) produced by the AGE-RAGE pathway as well as angiotensin II created in the RAS system [38,39]. Angiotensin II has both inflammatory and thrombotic properties, which are prominent findings in patients with COVID-19. Angiotensin II ignites the inflammatory reactions through the Angiotension 1 (AT1) receptor along with induction of RAGE expression by endothelial cells [12,40]. It can be postulated that the down-regulation of ACE2 by SARS-CoV-2[41,42] may lead to angiotensin II accumulation[42] which may further trigger the inflammatory reaction through the RAGE pathway. Considering the cross-talk between the AGE-RAGE pathway and the RAS system also the role of RAGE in the pathogenesis of severe form of COVID-19 [14,43], AGE-RAGE interaction may affect COVID-19 death through its impact on the RAS system that regulates blood pressure, which needs to be documented[43].

3.3. Obesity

Obesity is a risk factor for various diseases, including metabolic, kidney, and cardiovascular disorders [44]. Recently, it has been reported that obese individuals show a poor prognosis for COVID-19, such as the need for hospitalization and ventilation, in addition to respiratory failure [45-47]. The recent study reported a significant relationship between obesity and ICU admission in COVID-19 patients[47,48]. Additionally, obesity-related complications such as type 2 diabetes mellitus (T2DM) and hypertension are independent risk factors for a severe form of COVID-19 [48,49]. There is a close relation between RAGE, adiposity, and innate immune system activation[50,51]. It has been documented that inhibition of RAGE signaling may have therapeutic implications for obesity and metabolic disorders[52]. Furthermore, the reduction of methylglyoxal (MGO), one of the precursors of AGEs, has been shown to reduce obesity in mice. Dietary genistein reduces MGO and advanced glycation end-product accumulation in obese mice treated with a high-fat diet [53]. Gaens et al. confirmed the high expression of carboxymethyl lysine-AGE and RAGE receptor in adipocytes[54]. The AGE-RAGE interaction on the surface of adipocyte and macrophages in white adipocyte tissue induces the inflammatory cascade mediated by nuclear factor kappa B (NF-κB), which leads to cytokine and chemokine production[51]. It seems that the AGE-RAGE interaction in adipocytes may exacerbate the inflammatory reactions that occur in COVID-19 obese individuals, which need to be documented.

3.4. Diabetes and hyperglycemia

Data showed a remarkable association between diabetes mellitus and hyperglycemia with COVID-19 severity and increased mortality[55]. The study conducted by Codo et al. revealed that elevated glucose levels and enhanced glycolysis promotes SARS-CoV-2 replication and cytokine elaboration in monocytes [56]. Parallel to these findings, evidence showed that Glucose-lowering drugs routinely used to control blood sugar might reduce COVID-19 severity[55,57]. Increased blood glucose promotes inflammatory reactions through the generation of AGE compounds [58]. The accumulation of AGEs is associated with an increased risk of morbidity and mortality in diabetic patients [10]. AGEs are not merely biomarkers of a hyperglycemic and pro-inflammatory condition; rather, they also contribute to the pathogenesis of diabetic complications, such as peripheral neuropathy, nephropathy, and cardiomyopathy, mainly through their interactions with their principal receptor, RAGE[25,59-61]. AGEs are produced not only from glucose but also from intermediary molecules produced during glycolysis. Methylglyoxal (MGO) is non-enzymatically generated during glycolysis and is a critical precursor for several AGEs [10]. A recent study showed that SARS-CoV-2 induces glycolysis gene at the transcriptional levels at 24 post-infection to provide one-carbon metabolism necessary for its replication[62]. It can be postulated that striking induction of glycolysis reported in recent studies may expedite the production of AGEs during the initial phase of SARS-CoV-2 replication, especially in diabetic and hyperglycemic patients. AGEs up-regulates the expression of its receptor, RAGE, on the surface of endothelial cells, and its subsequent interactions with RAGE can induce exaggerated inflammatory and oxidative reactions through the elaboration of pro-inflammatory cytokines, including TNF-α, IL-1, and IL-6, and production of reactive oxygen and nitrogen intermediates respectively which may lead to endothelial dysfunction and hypercoagulation[58,63]. Considering the similarity between mechanistic principles that underlie a critical form of COVID-19 and the inflammation provoked by AGE and RAGE interaction, as well as the effect of the diabetes mellitus on COVID-19 severity, it can be hypothesized that diabetes mellitus can affect COVID-19 exacerbation through the accelerating the formation of AGE compounds. On the other hand, SARS-CoV-2 promotes glycolytic reactions that may serve as a source for amplification of AGEs production[62].

4. AGEs, cellular senescence and inflammaging

The chronic sterile low-grade Inflammation that occurs with age is defined as inflammaging [64]. A principal feature of inflammaging is the persistent activation of the innate immune system, in which the macrophage has a pivotal role [61]. A couple of self and non-self-molecules, including microbial pathogens, microbiota, nutrients, and damaged-associated molecules (DAMPs), underpin the inflammaging process through the activation of PRR receptors such as Toll-like receptors (TLRs) and induce the production of pro-inflammatory cytokines during inflammaging [64].

Experimental and epidemiological studies show that AGEs have a particular role in inflammaging through several mechanisms, including protein cross-linking, oxidative stress, senescence, and up-regulation of inflammatory processes [10,65]. As mentioned, above through binding several ligands, RAGE acts like a classic PRR and induces various subtle inflammatory reactions during the aging phenomenon [7,21]. Furthermore, AGEs can also contribute to inflammaging by increasing cellular

senescence. Cellular senescence, a state of stable growth arrest is accompanied by activation of inflammatory processes. Senescent cells increase with age in most mammalian tissues and can accelerate age-related diseases in part by secreting a myriad of factors, including pro-inflammatory molecules, collectively known as the senescence-associated secretory phenotype (SASP)[66,67]. A recent review discusses how increased cellular senescence may contribute to the cytokine storm observed in COVID-19 infections[68,69].

5. Ages in acute respiratory distress syndrome (ARDS) and sepsis

Acute respiratory distress syndrome (ARDS) is the potentially life-threatening inflammatory involvement of alveoli, which has a critical role in the COVID-19 associated death[70]. The alveolar macrophages and alveolar epithelial cells (AECs), including type1 and type 2 cells, have a pivotal role in the evolution of this respiratory syndrome [71,72]. The pattern recognition receptors, including TLRs, inflammasome, and RAGE, play pivotal roles in inflammatory reactions associated with ARDS and lung injury through their interactions with several pathogens associated molecular pattern (PAMP) and damaged-associated molecules (DAMPs) [73,74] (Fig. 2). Recently, it was shown that the expression of EN-RAGE (S100A12), a ligand for RAGE and a biomarker of pulmonary injury, strikingly increases in peripheral monocyte of COVID-19 patients and may promote pulmonary damage in these patients through its interaction with RAGE on the surface of alveolar epithelial cells [43]. This study accentuates the importance of RAGE and its ligand in the pathogenesis of COVID-19-associated lung injury. AGEs are one of the classical and primary ligands recognized for RAGEs [12,21]. The production and accumulation of AGEs in the body, due to physiological or pathological processes like aging and hyperglycemia, may promote COVID-19 related lung pathology in the elderly [10]. The existing data reveals that a diet with a high content of AGEs worsens acute lung injury in animal models [75].

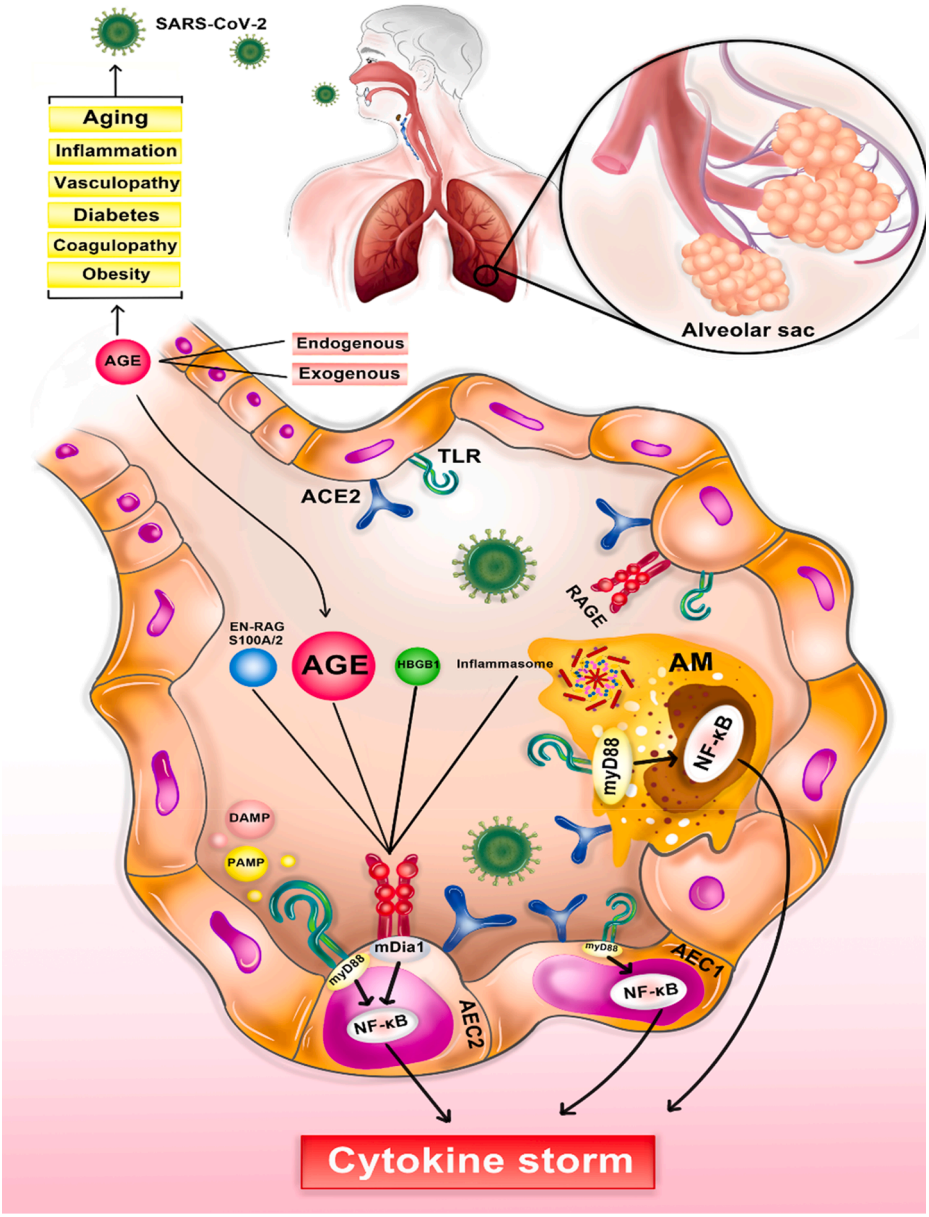

Fig 2. Contribution of AGEs in cytokine storm related to COVID-19 pathogenies. Different receptors and cells in alveolar sac are involved in cytokine storm syndrome. ACE2 as COVID-19 receptor is expressed on various cells including type one and type two alveolar epithelial cells as well as alveolar macrophages. On the other hand, RAGE receptor on the type 2 alveolar epithelial cells surface reacts with its ligands especially AGEs resulting to NF-κB activation and Cytokine storm.

Inflammasomes are multi-subunit and complex molecules, which induce the production of an active form of inflammatory cytokines, including IL-1 and IL-18, following activation by various molecules such as bacterial and viral pathogens [76]. Recent studies showed the importance of inflammasome in the development of the severe and critical form of COVID-19 [77-79]. Also, there is a close interaction between inflammasomes and RAGE in inflammatory diseases [80-82]. Considering these findings, one can postulate that the RAGE–AGE and inflammasome pathways may exert a significant role in the severe form of pneumonitis and determining the extent of lung damage in many pathological events, including severe pneumonitis in COVID-19 [82].

A previous study showed that patients with COVID-19 meet the diagnostic criteria for viral sepsis and septic shock [6]. Furthermore. RAGE signaling has a remarkable effect on the development of sepsis, and inhibition of this molecule with antibody (anti-RAGE) may mitigate the sepsis complications [83]. Thus the RAGE-AGE pathway is a potential contributor in COVID-19 associated septic, which needs to be further examined.

6. Anti-AGEs interventions that hypothetically could be used to minimize COVID-19 complications

Considering the association of AGEs with immune function, aging, and COVID-19 comorbidity diseases, AGEs can be a promising therapeutic target for treating patients with pre-existing conditions and severe COVID-19 symptoms. Studies that targeted AGEs for treating age-associated diseases have shown significant improvement in overall health in both animal models and human clinical trials [84]. Hence, inhibition of AGEs can be an alternate method for reducing the risk of COVID-19 and related mortalities.

Metformin is the cornerstone drug for the management of hyperglycemia in T2DM patients. Interestingly a recent study documented the positive effects of metformin, independent of its glucose reducing capabilities, in COVID-19 patients [85]. Data shows that metformin reduces the toxic effects of AGEs and reduces diabetes-associated COVID-19 severity. Association of Cardio Vascular Diseases (CVD) with COVID −19 is clinically proven, and pre-existing CVD conditions worsen the outcome of this viral disease [86]. Algaebrium chloride (ALT-711), a drug used for treating CVD, has shown promising results in breaking AGEs cross-linking and thus improving the heart condition in dogs [87], monkeys [88], diabetic mice models [89], and humans [90]. ALT-711 treatment improves cardiovascular functions by reducing ventricle stiffness. This drug was also proven to reduce the accumulation of carboxymethyl lysine (one of the AGEs) and increase the solubility of collagen [89]. Another drug C16 is proved for its ability to limit the accumulation of AGEs in blood vessels and prevent the AGEs cross-linking in the diabetic rat model [91]. Furthermore, aminoguanidine has shown a promising effect to improve vascular elasticity, permeability and reduce complications associated with cardiac hypertrophy in diabetic mice models. Notably, aminoguanidine treatment reduced the level of AGEs in diabetes and atherosclerosis mice models [89]. Reducing AGEs has proven to be an effective treatment for improving age-associated diabetes and cardiovascular diseases [92]. Taken together, it is compelling to hypothesize that reducing AGEs through the administration of the above drugs candidates could help to maintain cardiac function during SARS-CoV-2 infections.

Increased oxidative stress leads to the accumulation of AGEs and inflammatory disease, which has been observed in patients with Rheumatoid arthritis. Treatment with Pyridoxamine and Benfotiamine has proven to reduce the accumulation of AGEs in arthritis patients and improve the inflammatory condition [93]. In the case of SARS-CoV-2 infection excessive ROS is generated due to impaired redox balance in high-risk patients. Treatment with antioxidants is expected to regain the redox balance [94]. Given the role of AGEs to induce ROS, it will be interesting to see if Pyridoxamine and Benfotiamine have a positive impact in reducing the redox imbalance in COVID-19 patients.

Also, there is an alarming concern of acute renal failure in COVID-19 patients due to excessive cytokine release, which requires intensive care in critically ill patients. Clinicians are finding it problematic to manage acute renal failure and reduce mortality. The reason behind the renal failure in COVID-19 patients remains unclear for now [95]. Similar to these observations accumulation of AGEs are the causative factor in diabetic nephropathy that results in glomerular hypertrophy and reduced urine excretion [96]. In a treatment approach, short fragments of nucleic acids (DNA or RNA) called aptamers are reported to bind with AGEs and decrease the accumulation of AGEs in the kidney of diabetic mice. The binding of aptamers to AGEs facilitates effective removal of AGEs from the system and protects the kindney from the AGEs induced oxidative stress [96]. Considering the risk of renal failure in COVID-19 patients, these AGEs reducing aptamers could be considered for treating patients with renal damage.

7. Reducing AGE precursors to combat COVID-19

An alternate way to reduce AGEs is to target precursors of AGEs, the reactive carbonyls, generated as a byproduct of normal glycolysis. These reactive carbonyl compounds irreversibly modify nucleic acids and proteins through a non-enzymatic reaction. Reducing the reactivity of these dicarbonyls has proved to reduce the accumulation of AGEs. Methylglyoxal (MGO) is considered a major dicarbonyl that can react with biological macromolecules to generate different AGEs. Carnisone is a naturally occurring dipeptide that is proven to effectively inhibit the activity of methylglyoxal *in vitro* [97]. Carnisone is effective not only against AGEs generated through glycolysis but also against aldehydes generated through lipid peroxidation [98]. This drug has been proven to negate several health complications including hyperglycemia. Similar to carnisone other peptides like homocarnisone and anserine are found to reduce the glycation process and thereby limit the generation of AGEs [99]. As these peptides are naturally occurring and proven to be safe, exploring the effectiveness of these peptides for COVID-19 treatment might serve as an alternate way to reduce the generation of AGEs and their secondary complication in patients.

LR90 is another potent inhibitor of MGO-induced cytotoxicity and serves as a potent antioxidant and anti-inflammatory drug. LR90 exhibits cytoprotective activity against MGO-induced apoptosis by preventing the release of cytochrome *C* and inhibiting the activation of caspase-3 and caspase-9 [100]. A recent study reported that SARS-CoV-2 infection-induced apoptosis through its accessory protein ORF3a in a similar pathway of activating the release of mitochondrial cytochrome *C* and activation of caspase-9 [101]. The close correlation between the pathways involved in MGO cytotoxicity and SARS-Cov-2 infection mediated cytotoxicity is striking. Hence, LR90 could be a potential drug candidate to reduce cytotoxicity in COVID-19 patients through its effects on AGEs. Analogous to LR90, antioxidants like aminoguanidine and N-acetyl cysteine are proved to better combat the cytotoxic effects of MGO in endothelial cells [102].

8. Inhibiting RAGE axis to limit COVID-19 related inflammation

Upon activation by ligands, RAGE initiates series of pathways that end up in the generation of ROS and inflammation response. RAGE-mediated activation of pro-inflammatory signals results in tissue damage and regulation of NADPH oxidase that contributes to oxidative stress and neutrophil dysfunction [10]. Given the expression of RAGE in lungs and the critical role of ACE-2 receptors in alveolar cells for SARS-CoV-2 binding, there is a higher possibility for AGE-RAGEs to be involved in COVID-19 progression. Several small molecules have been tested for their efficacy to inhibit RAGE [103]. TTP488, also known as Azeliragon, inhibits the binding of several RAGE ligands, including HMGB1, S100B, and Aβ [104]. TTP488 treatment reduces inflammatory signaling in neurodegenerative models. At a low dose of 5 μM, this drug was found to be not only safe but also improve cognitive function in human subjects

[105]. HMGB1 and S100 protein families are the damage-associated signal that are highly expressed in diabetes and microbial infections. A recent clinical study in COVID-19 patients revealed that HMGB1 and S100 A8/A9 levels were significantly high in severe infections. This was found to be associated with poor clinical outcomes, including infection-related tissue damage and cytokine storm [106]. Another small molecule FPS-ZM1, initially identified to inhibit the RAGE-Aβ interaction, was also found to reduce inflammatory signaling in mouse models. FPS-ZM1 effective in rescuing cardiac dysfunction, hypertrophy, and inflammation [107]. Pyrazole-5-carboxamides and 6-Phenoxy-2-phenylbenzoxazoles are other serirs of RAGE inhibitors, exhibited RAGE inhibitory activity in previous studies[108,109]. Given the efficiency of these drugs to limit RAGE activation by its ligands and their role in reducing inflammatory responses, it will worth studying their effect to reduce COVID-19 associated disease outcomes.

9. Reducing dietary AGEs to limit COVID-19 associated inflammation

Dietary or exogenous AGEs are the primary source of AGE molecules in our body[110]. Exogenous AGEs are mainly produced during heat-processing of foods by non-enzymatic Maillard reaction between free carbonyl groups[111]. AGEs are effectively absorbed in the gastrointestinal system, and there is a direct association between plasma AGEs concentrations and dietary AGEs intake and its elimination by kidneys [112,113]. Data from clinical trials accentuate the critical role of the high dietary intake of AGEs molecules in triggering and promoting inflammatory and oxidative reactions[110,114]. There are several approaches for reducing the dietary AGEs including, lowering the cooking temperature, decreasing cooking time, and using higher humidity and moisture during food preparation, caloric restriction is another way for diminishing exogenous AGEs [115-118]. Fats and meats tend to contain more dietary AGE per gram of weight, given that reducing butter, cream cheese, margarine, beef, and hamburger in a routine regimen can help lessen exogenous AGEs. On the other hand, foods such as low-fat milk, vegetables, yogurt, natural juice, honey, chicken, and lamb have low exogenous AGE content[118]. Reducing dietary AGEs content in routine regimen during the pandemic period by simple modifications may hypothetically be beneficial for blunting the hyperinflammatory mechanisms underlying the pathogenesis of a severe form of COVID-19.

Although the direct role of AGEs and RAGE in COVID-19 disease progression and severity is yet to be clarified there seems to be more correlation between AGEs and COVID-19 pathogenicity. Given the uncertainty of potent vaccine or drug candidates against COVID-19 it is worth testing the biomolecules that can potentially reduce the burden of AGEs as complementary treatment (Table 1), to minimize the effect of COVID-19 infections.

10. Conclusion

Given the association of COVID-19 with various underlying conditions and clinical manifestations, finding molecules with the crucial contribution in all aspects of COVID-19 exacerbation can open a new window for the treatment of this substantial global concern. Regarding important influences of AGEs on aging as the most significant risk factor for the severe form of COVID-19 and its apparent association with COVID-19-associated risk factor, including hypertension, obesity, diabetes, cardiovascular and renal disease, as well as inflammaging, the study of AGEs and their effects on COVID-19 death could potentially provide more helpful clues about the mechanism of tissue injuries in COVID-19, and also may help to provide dietary and treatment interventions to reduce the mortality of this pandemic emergency. The strong overlap between pathways regulated by AGEs and COVID-19, argue that drugs that are effective against AGEs would be potential drug candidates to treat COVID-19 and associated diseases.

Table 1
Potential therapeutics to interven the AGE-RAGE signaling in COVID-19 patients and improve clinical outcomes.

S. No	Compound/Drug	Mechanism of Action
1	Metformin	Anti-inflammatory
2	Algaebrium chloride	Improves cardiac function, reduce collagen crosslinking
3	Carnisone	Inhibits Methylglyoxal
4	Homocarnisobe	Reduce glycation process
5	Anserine	Reduce glycation process
6	LR90	Inhibits MGO induced cytotoxicity
7	Amino guanidine	Inhibits MGO induced cytotoxicity
8	N-acetyl cystine (NAC)	Inhibits MGO induced cytotoxicity
9	Azeliragon (TTP488)	RAGE innhibitor
10	FPS-ZM1	RAGE innhibitor
11	Pyrazole-5-carboxamides	RAGE inhibitors
12	6-Phenoxy-2-phenylbenzoxazoles	RAGE inhibitors
13	Pyridoxine	RAGE signaling Inhibitor
14	Flavonoids	Enhances the Glyoxalase Pathway
15	DNA RNA aptamers	Reduce AGEs induced stress and removal of AGEs
16	B alanine	Reduce glycation process
17	Histidine	Reduce glycation process
18	3-[2-(4-Bromo-phenyl)-1-methyl-2-oxo-ethyl]-4,5,6,7-tetrahydro-benzothiazol-3-ium bromide (C16)	Reduce AGEs accumulation

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] C. Huang, Y. Wang, X. Li, L. Ren, J. Zhao, Y. Hu, et al., Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 395 (10223) (2020) 497–506.
[2] N. Chen, M. Zhou, X. Dong, J. Qu, F. Gong, Y. Han, et al., Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study, Lancet 395 (10223) (2020) 507–513.
[3] S. Moradinasab, A. Pourbagheri-Sigaroodi, P. Zafari, S.H. Ghaffari, D. Bashash, Mesenchymal stromal/stem cells (MSCs) and MSC-derived extracellular vesicles in COVID-19-induced ARDS: Mechanisms of action, research progress, challenges, and opportunities, Int. Immunopharmacol. 97 (2021), 107694.
[4] G. Deng, M. Yin, X. Chen, F.J. Zeng, Clinical determinants for fatality of 44,672 patients with COVID-19, Crit care. 24 (1) (2020) 1–3.
[5] E.J. Williamson, A.J. Walker, K. Bhaskaran, S. Bacon, C. Bates, C.E. Morton, et al., Factors associated with COVID-19-related death using OpenSAFELY, Nature 584 (7821) (2020) 430–436.
[6] W.C. Koff, M.A. Williams, Covid-19 and immunity in aging populations—a new research agenda, N. Engl. J. Med. 383 (9) (2020) 804–805.
[7] C. Franceschi, J.J. Campisi, M. Sciences, Chronic inflammation (inflammaging) and its potential contribution to age-associated diseases, J. Gerontol. A Biol. Sci. Med. Sci. 69 (Suppl_1) (2014) S4–S9.
[8] M.Z. Tay, C.M. Poh, L. Rénia, P.A. MacAry, L.F. Ng, The trinity of COVID-19: immunity, inflammation and intervention, Nat. Rev. Immunol. (2020) 1–12.
[9] M. Bonafè, F. Prattichizzo, A. Giuliani, G. Storci, J. Sabbatinelli, F.J.C. Olivieri, et al., Inflamm-aging: Why older men are the most susceptible to SARS-CoV-2 complicated outcomes, Cytokine Growth Factor Rev. 54 (2020) 1–2.
[10] J. Chaudhuri, Y. Bains, S. Guha, A. Kahn, D. Hall, N. Bose, et al., The Role of Advanced Glycation End Products in Aging and Metabolic Diseases: Bridging Association and Causality, Cell Metab. 28 (3) (2018) 337–352.

[11] C. Wang, J. Xie, L. Zhao, X. Fei, H. Zhang, Y. Tan, et al., Alveolar macrophage dysfunction and cytokine storm in the pathogenesis of two severe COVID-19 patients, EBioMedicine. 57 (2020), 102833.
[12] B.I. Hudson, M.E. Lippman, Targeting RAGE signaling in inflammatory disease, Annu. Rev. Med. 69 (2018) 349–364.
[13] A.A. van Beek, J. Van den Bossche, P.G. Mastroberardino, M.P. de Winther, P. J. Leenen, Metabolic alterations in aging macrophages: ingredients for inflammaging? Trends Immunol. 40 (2) (2019) 113–127.
[14] D. Yalcin Kehribar, M. Cihangiroglu, E. Sehmen, B. Avci, A. Capraz, A. Yildirim Bilgin, et al., The Receptor for Advanced Glycation End Product (RAGE) Pathway in COVID-19, Biomarkers 1–17 (2020).
[15] K. Byun, Y. Yoo, M. Son, J. Lee, G.-B. Jeong, Y.M. Park, et al., Advanced glycation end-products produced systemically and by macrophages: A common contributor to inflammation and degenerative diseases, Pharmacol. Ther. 177 (2017) 44–55.
[16] S. Chiappalupi, L. Salvadori, A. Vukasinovic, R. Donato, G. Sorci, F. Riuzzi, Targeting RAGE to prevent SARS-CoV-2-mediated multiple organ failure: Hypotheses and perspectives, Life Sci. 119251 (2021).
[17] A. Lim, A. Radujkovic, M.A. Weigand, U. Merle, Soluble receptor for advanced glycation end products (sRAGE) as a biomarker of COVID-19 disease severity and indicator of the need for mechanical ventilation, ARDS and mortality, Ann. Intensive Care. 11 (1) (2021) 1–13.
[18] R.D. Semba, E.J. Nicklett, L.J. Ferrucci, M. Sciences, Does accumulation of advanced glycation end products contribute to the aging phenotype? J. Gerontol. A Biol. Sci. Med. Sci. 65 (9) (2010) 963–975.
[19] A.S. Kiefer, T. Fleming, G.J. Eckert, B.B. Poindexter, P.P. Nawroth, M.C.J.P. R. Yoder, Methylglyoxal concentrations differ in standard and washed neonatal packed red blood cells, Pediatr. Res. 75 (3) (2014) 409–414.
[20] A.M. Schmidt, M. Vianna, M. Gerlach, J. Brett, J. Ryan, J. Kao, et al., Isolation and characterization of two binding proteins for advanced glycosylation end products from bovine lung which are present on the endothelial cell surface, J. Biol. Chem. 267 (21) (1992) 14987–14997.
[21] G.J. Fritz, RAGE: a single receptor fits multiple ligands, Trends Biochem. Sci. 36 (12) (2011) 625–632.
[22] G. Daffu, C.H. Del Pozo, K.M. O'Shea, R. Ananthakrishnan, R. Ramasamy, A. M. Schmidt, Radical roles for RAGE in the pathogenesis of oxidative stress in cardiovascular diseases and beyond, Int. J. Mol. Sci. 14 (10) (2013) 19891–19910.
[23] H. Ejaz, A. Alsrhani, A. Zafar, H. Javed, K. Junaid, A.E. Abdalla, et al., COVID-19 and comorbidities: Deleterious impact on infected patients, J. Infect. Public Health. 13 (12) (2020) 1833–1839.
[24] S. Richardson, J.S. Hirsch, M. Narasimhan, J.M. Crawford, T. McGinn, K. W. Davidson, et al., Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area, JAMA 323 (20) (2020) 2052–2059.
[25] V.M. Monnier, N. Taniguchi, Advanced glycation in diabetes, aging and age-related diseases: editorial and dedication, Glycoconj J. 33 (4) (2016) 483–486.
[26] R.D. Semba, S. Bandinelli, K. Sun, J.M. Guralnik, L.J. Ferrucci, Plasma carboxymethyl-lysine, an advanced glycation end product, and all-cause and cardiovascular disease mortality in older community-dwelling adults, J. Am. Geriatr. Soc. 57 (10) (2009) 1874–1880.
[27] R.D. Semba, E.J. Nicklett, L. Ferrucci, Does accumulation of advanced glycation end products contribute to the aging phenotype? J. Gerontol. A Biol. Sci. Med. Sci. 65 (9) (2010) 963–975.
[28] M. Kerkeni, J. Gharbi, RAGE receptor: May be a potential inflammatory mediator for SARS-COV-2 infection? Med. Hypotheses. Med. Hypotheses. 144 (2020), 109950.
[29] A. Rojas, I. Gonzalez, M.A. Morales, SARS-CoV-2-mediated inflammatory response in lungs: should we look at RAGE? Inflamm. Res. 69 (7) (2020) 641–643.
[30] J. Ran, Y. Song, Z. Zhuang, L. Han, S. Zhao, P. Cao, et al., Blood pressure control and adverse outcomes of COVID-19 infection in patients with concomitant hypertension in Wuhan, China, Hypertens Res. (2020) 1–10.
[31] F. Zhou, T. Yu, R. Du, G. Fan, Y. Liu, Z. Liu, et al., Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study, Lancet 395 (10229) (2020) 1054–1062.
[32] M.A. Ondetti, D.W. Cushman, Inhibition of the renin-angiotensin system. A new approach to the therapy of hypertension, J. Med. Chem. 24 (4) (1981) 355–361.
[33] A. Renieri, E. Benetti, R. Tita, O. Spiga, A. Ciolfi, G. Birolo, et al., ACE2 variants underlie interindividual variability and susceptibility to COVID-19 in Italian population, Nature 28 (2020) 1602–1614.
[34] M. Donoghue, F. Hsieh, E. Baronas, K. Godbout, M. Gosselin, N. Stagliano, et al., A novel angiotensin-converting enzyme–related carboxypeptidase (ACE2) converts angiotensin I to angiotensin 1–9, Circ. Res. 87 (5) (2000) e1–e9.
[35] C. Tikellis, M. Thomas, Angiotensin-converting enzyme 2 (ACE2) is a key modulator of the renin angiotensin system in health and disease, Int. J. Peptides. 2012 (2012).
[36] F. Warner, A. Smith, N. Hooper, A. Turner, Angiotensin-converting enzyme-2: a molecular and cellular perspective, Cellular Mol. Life Sci.: CMLS. 61 (21) (2004) 2704–2713.
[37] P. Zhou, X.-L. Yang, X.-G. Wang, B. Hu, L. Zhang, W. Zhang, et al., A pneumonia outbreak associated with a new coronavirus of probable bat origin, Nature 579 (7798) (2020) 270–273.
[38] C.L. Cheng, Y. Tang, Z. Zheng, X. Liu, C.Y. Zengchun, C. Wang, et al., Advanced glycation end-products activate the renin-angiotensin system through the RAGE/PI3-K signaling pathway in podocytes, Clin. Invest. Med. (2012) E282–E293.
[39] S-i Yamagishi, M. Takeuchi, T. Matsui, K. Nakamura, T. Imaizumi, H. Inoue, Angiotensin II augments advanced glycation end product-induced pericyte apoptosis through RAGE overexpression, FEBS Lett. 579 (20) (2005) 4265–4270.
[40] S. Vasdev, V. Gill, P.J. Singal, Role of advanced glycation end products in hypertension and atherosclerosis: therapeutic implications, Cell Biochem. Biophys. 49 (1) (2007) 48–63.
[41] M.M. Ciulla, SARS-CoV-2 downregulation of ACE2 and pleiotropic effects of ACEIs/ARBs, Hypertens. Res. 43 (9) (2020) 985–986.
[42] H.R. Reynolds, S. Adhikari, C. Pulgarin, A.B. Troxel, E. Iturrate, S.B. Johnson, et al., Renin–angiotensin–aldosterone system inhibitors and risk of Covid-19, N. Engl. J. Med. 382 (25) (2020) 2441–2448.
[43] P.S. Arunachalam, F. Wimmers, C.K.P. Mok, R.A. Perera, M. Scott, T. Hagan, et al., Systems biological assessment of immunity to mild versus severe COVID-19 infection in humans, Science 369 (6508) (2020) 1210–1220.
[44] C. Eleazu, N. Omar, O.Z. Lim, B.S. Yeoh, N.H. Nik Hussain, M. Mohamed, Obesity and Comorbidity: Could Simultaneous Targeting of esRAGE and sRAGE Be the Panacea? Frontiers in physiology. 2019;10:787-.
[45] R.W. Alberca, Ld.M. Oliveira, A.C.C.C. Branco, N.Z. Pereira, M.N. Sato, Obesity as a risk factor for COVID-19: an overview, Crit. Rev. Food Sci. Nutr. (2020) 1–15.
[46] B.M. Popkin, S. Du, W.D. Green, M.A. Beck, T. Algaith, C.H. Herbst, et al., Individuals with obesity and COVID-19: A global perspective on the epidemiology and biological relationships, Obes. Rev. 21 (11) (2020), e13128.
[47] M. Gao, C. Piernas, N.M. Astbury, J. Hippisley-Cox, S. O'Rahilly, P. Aveyard, et al., Associations between body-mass index with severity of SARS-CoV-2 infection in a community-based cohort of 6.9 million people in England, Lancet Diabet. Endocrinol. (2021) 2–5.
[48] Y. Shi, X. Yu, H. Zhao, H. Wang, R. Zhao, J.J. Sheng, Host susceptibility to severe COVID-19 and establishment of a host risk score: findings of 487 cases outside Wuhan, Crit Care. 24 (1) (2020) 1–4.
[49] C. Caussy, F. Pattou, F. Wallet, C. Simon, S. Chalopin, C. Telliam, et al., Prevalence of obesity among adult inpatients with COVID-19 in France, Lancet Diabetes Endocrinol. 8 (7) (2020) 562–564.
[50] M. Monden, H. Koyama, Y. Otsuka, T. Morioka, K. Mori, T. Shoji, et al., Receptor for advanced glycation end products regulates adipocyte hypertrophy and insulin sensitivity in mice: involvement of Toll-like receptor 2, Diabetes 62 (2) (2013) 478–489.
[51] Z. Feng, L. Zhu, J. Wu, RAGE signalling in obesity and diabetes: focus on the adipose tissue macrophage, Adipocyte. 9 (1) (2020) 563–566.
[52] F. Song, C.H. del Pozo, R. Rosario, Y.S. Zou, R. Ananthakrishnan, X. Xu, et al., RAGE regulates the metabolic and inflammatory response to high-fat feeding in mice, Diabetes 63 (6) (2014) 1948–1965.
[53] Y. Zhao, Y. Zhu, P. Wang, S. Sang, Dietary Genistein Reduces Methylglyoxal and Advanced Glycation End Product Accumulation in Obese Mice Treated with High-Fat Diet, J Agric Food Chem. 68 (28) (2020) 7416–7424.
[54] K.H. Gaens, G.H. Goossens, P.M. Niessen, M.M. van Greevenbroek, C.J. van der Kallen, H.W. Niessen, et al., Nε-(carboxymethyl) lysine-receptor for advanced glycation end product axis is a key modulator of obesity-induced dysregulation of adipokine expression and insulin resistance, Arterioscler. Thromb. Vasc. Biol. 34 (6) (2014) 1199–1208.
[55] S. Lim, J.H. Bae, H.-S. Kwon, M.A. Nauck, COVID-19 and diabetes mellitus: from pathophysiology to clinical management. Nature Reviews, Endocrinology (2020) 1–20.
[56] A.C. Codo, G.G. Davanzo, Monteiro L de Brito, G.F. de Souza, S.P. Muraro, J. V. Virgilio-da-Silva, et al., Elevated glucose levels favor SARS-CoV-2 infection and monocyte response through a HIF-1α/glycolysis-dependent axis, Cell Metab. 32 (3) (2020), pp. 437–46. e5.
[57] C.T. Bramante, N.E. Ingraham, T.A. Murray, S. Marmor, S. Hovertsen, J. Gronski, et al., Metformin and risk of mortality in patients hospitalised with COVID-19: a retrospective cohort analysis, The Lancet Healthy Longevity. 2 (1) (2021) e34–e41.
[58] S.Y. Rhee, Y.S. Kim, The role of advanced glycation end products in diabetic vascular complications, Diabetes & Metabol. J. 42 (3) (2018) 188.
[59] R.C. Ma, Genetics of cardiovascular and renal complications in diabetes, J. Diabetes Investig. 7 (2) (2016) 139–154.
[60] V.P. Singh, A. Bali, N. Singh, A.S. Jaggi, Advanced glycation end products and diabetic complications, Korean J. Physiol. Pharmacol. 18 (1) (2014) 1–14.
[61] C. Franceschi, M. Bonafè, S. Valensin, F. Olivieri, M. De Luca, E. Ottaviani, et al., Inflamm-aging: an evolutionary perspective on immunosenescence, Ann. NY Acad. Sci. 908 (1) (2000) 244–254.
[62] Y. Zhang, R. Guo, S.H. Kim, H. Shah, S. Zhang, J.H. Liang, et al., SARS-CoV-2 hijacks folate and one-carbon metabolism for viral replication, Nat. Commun. 12 (1) (2021) 1–11.
[63] H. Wu, R. Li, L.-G. Pei, Z.-H. Wei, L.-N. Kang, L. Wang, et al., Emerging role of high mobility group box-1 in thrombosis-related diseases, Cell. Physiol. Biochem. 47 (4) (2018) 1319–1337.
[64] C. Franceschi, P. Garagnani, P. Parini, C. Giuliani, A.J. Santoro, Inflammaging: a new immune–metabolic viewpoint for age-related diseases, Nat. Rev. Endocrinol. 14 (10) (2018) 576–590.
[65] M. Tosato, V. Zamboni, A. Ferrini, M.J. Cesari, The aging process and potential interventions to extend life expectancy, Clin. Interv. Aging 2 (3) (2007) 401.
[66] J.-P. Coppé, P.-Y. Desprez, A. Krtolica, J. Campisi, The senescence-associated secretory phenotype: the dark side of tumor suppression, Annu. Rev. Pathol. 5 (2010) 99–118.
[67] D. McHugh, J. Gil, Senescence and aging: Causes, consequences, and therapeutic avenues, J. Cell Biol. 217 (1) (2018) 65–77.

[68] J. Nehme, M. Borghesan, S. Mackedenski, T.G. Bird, M. Demaria, Cellular senescence as a potential mediator of COVID-19 severity in the elderly. Aging Cell. 19, 10, e13237.
[69] C. Sargiacomo, F. Sotgia, M.P. Lisanti, COVID-19 and chronological aging: senolytics and other anti-aging drugs for the treatment or prevention of corona virus infection? Aging (Albany NY). 12 (8) (2020) 6511.
[70] D.A. Berlin, R.M. Gulick, F.J. Martinez, Severe Covid-19, N. Engl. J. Med. 383 (25) (2020) 2451–2460.
[71] S. Spadaro, M. Park, C. Turrini, T. Tunstall, R. Thwaites, T. Mauri, et al., Biomarkers for acute respiratory distress syndrome and prospects for personalised medicine, J. Inflamm. (Lond). 16 (1) (2019) 1.
[72] M.A. Matthay, R.L. Zemans, G.A. Zimmerman, Y.M. Arabi, J.R. Beitler, A. Mercat, et al., Acute respiratory distress syndrome, Nat. Rev. Dis. Primers. 5 (1) (2019) 1–22.
[73] W.A. Guo, P.R. Knight, K.J. Raghavendran, The receptor for advanced glycation end products and acute lung injury/acute respiratory distress syndrome, Intensive Care Med. 38 (10) (2012) 1588–1598.
[74] T. Dolinay, Y.S. Kim, J. Howrylak, G.M. Hunninghake, C.H. An, L. Fredenburgh, et al., Inflammasome-regulated cytokines are critical mediators of acute lung injury, Am. J. Respir. Crit. Care Med. 185 (11) (2012) 1225–1234.
[75] J. Ottosen, B. Mullan, P. Ohtake, B. Davidson, W. Guo, P.J. Knight, Diet high in advanced glycation end products exacerbates pulmonary inflammatory response and impairs lung compliance in mice following gastric aspiration, J. Surg. Res. (2010;158(2):214.).
[76] H. Guo, J.B. Callaway, J.P. Ting, Inflammasomes: mechanism of action, role in disease, and therapeutics, Nat. Med. 21 (7) (2015) 677–687.
[77] T.L. Freeman, T.H. Swartz, Targeting the NLRP3 inflammasome in severe COVID-19, Front. Immunol. 11 (2020) 1518.
[78] D.F. van den Berg, A.A. Te Velde, Severe COVID-19: NLRP3 inflammasome dysregulated, Front. Immunol. 11 (2020) 1580.
[79] S. Toldo, R. Bussani, V. Nuzzi, A. Bonaventura, A.G. Mauro, A. Cannatà, et al., Inflammasome formation in the lungs of patients with fatal COVID-19, Inflamm. Res. 70 (1) (2021) 7–10.
[80] C. Jia, J. Zhang, H. Chen, Y. Zhuge, H. Chen, F. Qian, et al., Endothelial cell pyroptosis plays an important role in Kawasaki disease via HMGB1/RAGE/cathespin B signaling pathway and NLRP3 inflammasome activation, Cell Death Dis. 10 (10) (2019) 1–16.
[81] W.-J. Yeh, H.-Y. Yang, M.-H. Pai, C.-H. Wu, J.-R. Chen, Long-term administration of advanced glycation end-product stimulates the activation of NLRP3 inflammasome and sparking the development of renal injury, J. Nutr. Biochem. 39 (2017) 68–76.
[82] S. Son, I. Hwang, J.W. Yu, Modulation of inflammasome signaling by advanced glycation end products (AGEs), FASEB J. 31 (2017) lb194-lb.
[83] E.C. Lutterloh, S.M. Opal, D.D. Pittman, J.C. Keith, X.-Y. Tan, B.M. Clancy, et al., Inhibition of the RAGE products increases survival in experimental models of severe sepsis and systemic infection, Crit. Care 11 (6) (2007) R122.
[84] P. Yang, J. Feng, Q. Peng, X. Liu, Z. Fan, Advanced Glycation End Products: Potential Mechanism and Therapeutic Target in Cardiovascular Complications under Diabetes, Oxid. Med. Cell Longev. 2019 (2019) 9570616.
[85] A.J. Scheen, Metformin and COVID-19: From cellular mechanisms to reduced mortality, Diabetes Metab. 46 (6) (2020) 423–426.
[86] M. Nishiga, D.W. Wang, Y. Han, D.B. Lewis, J.C. Wu, COVID-19 and cardiovascular disease: from basic mechanisms to clinical perspectives, Nat. Rev. Cardiol. 17 (9) (2020) 543–558.
[87] J. Liu, M.R. Masurekar, D.E. Vatner, G.N. Jyothirmayi, T.J. Regan, S.F. Vatner, et al., Glycation end-product cross-link breaker reduces collagen and improves cardiac function in aging diabetic heart, Am. J. Physiol. Heart Circ. Physiol. 285 (6) (2003) H2587–H2591.
[88] P.V. Vaitkevicius, M. Lane, H. Spurgeon, D.K. Ingram, G.S. Roth, J.J. Egan, et al., A cross-link breaker has sustained effects on arterial and ventricular properties in older rhesus monkeys, Proc. Natl. Acad. Sci. USA 98 (3) (2001) 1171–1175.
[89] J.M. Forbes, L.T. Yee, V. Thallas, M. Lassila, R. Candido, K.A. Jandeleit-Dahm, et al., Advanced glycation end product interventions reduce diabetes-accelerated atherosclerosis, Diabetes 53 (7) (2004) 1813–1823.
[90] D.A. Kass, E.P. Shapiro, M. Kawaguchi, A.R. Capriotti, A. Scuteri, R.C. deGroof, et al., Improved arterial compliance by a novel advanced glycation end-product crosslink breaker, Circulation 104 (13) (2001) 1464–1470.
[91] G. Cheng, L.L. Wang, W.S. Qu, L. Long, H. Cui, H.Y. Liu, et al., C16, a novel advanced glycation endproduct breaker, restores cardiovascular dysfunction in experimental diabetic rats, Acta Pharmacol. Sin. 26 (12) (2005) 1460–1466.
[92] K.C. Chang, C.D. Tseng, M.S. Wu, J.T. Liang, M.S. Tsai, Y.L. Cho, et al., Aminoguanidine prevents arterial stiffening in a new rat model of type 2 diabetes, Eur. J. Clin. Invest. 36 (8) (2006) 528–535.
[93] A. Syngle, K. Vohra, N. Garg, L. Kaur, P. Chand, Advanced glycation end-products inhibition improves endothelial dysfunction in rheumatoid arthritis, Int. J. Rheum. Dis. 15 (1) (2012) 45–55.
[94] M. Laforge, C. Elbim, C. Frere, M. Hemadi, C. Massaad, P. Nuss, et al., Tissue damage from neutrophil-induced oxidative stress in COVID-19, Nat. Rev. Immunol. 20 (9) (2020) 515–516.
[95] A. Raza, A. Estepa, V. Chan, M.S. Jafar, Acute Renal Failure in Critically Ill COVID-19 Patients With a Focus on the Role of Renal Replacement Therapy: A Review of What We Know So Far, Cureus. 12 (6) (2020), e8429.
[96] Y. Kaida, K. Fukami, T. Matsui, Y. Higashimoto, Y. Nishino, N. Obara, et al., DNA aptamer raised against AGEs blocks the progression of experimental diabetic nephropathy, Diabetes 62 (9) (2013) 3241–3250.
[97] A.R. Hipkiss, C. Brownson, M.J. Carrier, Carnosine, the anti-ageing, anti-oxidant dipeptide, may react with protein carbonyl groups, Mech. Ageing Dev. 122 (13) (2001) 1431–1445.
[98] S. Zhou, E.A. Decker, Ability of carnosine and other skeletal muscle components to quench unsaturated aldehydic lipid oxidation products, J. Agric. Food Chem. 47 (1) (1999) 51–55.
[99] M.A.C.B. Freund, E.A. Decker, The inhibition of advanced glycation end products by carnosine and other natural dipeptides to reduce diabetic and age-related complications, Compr. Rev. Food Sci. Food Saf. 17 (5) (2018) 1367–1378.
[100] J.L. Figarola, J. Singhal, S. Rahbar, S. Awasthi, S.S. Singhal, LR-90 prevents methylglyoxal-induced oxidative stress and apoptosis in human endothelial cells, Apoptosis 19 (5) (2014) 776–788.
[101] Y. Ren, T. Shu, D. Wu, J. Mu, C. Wang, M. Huang, et al., The ORF3a protein of SARS-CoV-2 induces apoptosis in cells, Cell Mol. Immunol. 17 (8) (2020) 881–883.
[102] S. Rahbar, Novel inhibitors of glycation and AGE formation, Cell Biochem. Biophys. 48 (2–3) (2007) 147–157.
[103] S. Bongarzone, V. Savickas, F. Luzi, A.D. Gee, Targeting the Receptor for Advanced Glycation Endproducts (RAGE): A Medicinal Chemistry Perspective, J. Med. Chem. 60 (17) (2017) 7213–7232.
[104] D. Galasko, J. Bell, J.Y. Mancuso, J.W. Kupiec, M.N. Sabbagh, C. van Dyck, et al., Clinical trial of an inhibitor of RAGE-Abeta interactions in Alzheimer disease, Neurology. 82 (17) (2014) 1536–1542.
[105] A.H. Burstein, I. Grimes, D.R. Galasko, P.S. Aisen, M. Sabbagh, A.M. Mjalli, Effect of TTP488 in patients with mild to moderate Alzheimer's disease, BMC Neurol. 14 (2014) 12.
[106] L. Chen, X. Long, Q. Xu, J. Tan, G. Wang, Y. Cao, et al., Elevated serum levels of S100A8/A9 and HMGB1 at hospital admission are correlated with inferior clinical outcomes in COVID-19 patients, Cell Mol. Immunol. 17 (9) (2020) 992–994.
[107] R. Deane, I. Singh, A.P. Sagare, R.D. Bell, N.T. Ross, B. LaRue, et al., A multimodal RAGE-specific inhibitor reduces amyloid beta-mediated brain disorder in a mouse model of Alzheimer disease, J. Clin. Invest. 122 (4) (2012) 1377–1392.
[108] Y.T. Han, K. Kim, G.-I. Choi, H. An, D. Son, H. Kim, et al., Pyrazole-5-carboxamides, novel inhibitors of receptor for advanced glycation end products (RAGE), Eur. J. Med. Chem. 79 (2014) 128–142.
[109] K. Choi, K.S. Lim, J. Shin, S.H. Kim, Y.-G. Suh, H.-S. Hong, et al., 6-Phenoxy-2-phenylbenzoxazoles, novel inhibitors of receptor for advanced glycation end products (RAGE), Bioorg. Med. Chem. 23 (15) (2015) 4919–4935.
[110] N.J. Kellow, G.S. Savige, Dietary advanced glycation end-product restriction for the attenuation of insulin resistance, oxidative stress and endothelial dysfunction: a systematic review, Eur. J. Clin. Nutr. 67 (3) (2013) 239–248.
[111] F.J. Tessier, I. Birlouez-Aragon, Health effects of dietary Maillard reaction products: the results of ICARE and other studies, Amino Acids 42 (4) (2012) 1119–1131.
[112] C. Delgado-Andrade, F.J. Tessier, C. Niquet-Leridon, I. Seiquer, M.P. Navarro, Study of the urinary and faecal excretion of N ε-carboxymethyllysine in young human volunteers, Amino Acids 43 (2) (2012) 595–602.
[113] N. Tahara, Yamagishi Si, T. Matsui, M. Takeuchi, Y. Nitta, N. Kodama, et al., Serum levels of advanced glycation end products (AGEs) are independent correlates of insulin resistance in nondiabetic subjects, Cardiovasc. Ther. 30 (1) (2012) 42–48.
[114] K. Nowotny, D. Schröter, M. Schreiner, T. Grune, Dietary advanced glycation end products and their relevance for human health, Ageing Res. Rev. 47 (2018) 55–66.
[115] S.M. Hofmann, H.-J. Dong, Z. Li, W. Cai, J. Altomonte, S.N. Thung, et al., Improved insulin sensitivity is associated with restricted intake of dietary glycoxidation products in the db/db mouse, Diabetes 51 (7) (2002) 2082–2089.
[116] J. Feng, F. Hou, M. Liang, G. Wang, X. Zhang, H. Li, et al., Restricted intake of dietary advanced glycation end products retards renal progression in the remnant kidney model, Kidney Int. 71 (9) (2007) 901–911.
[117] W. Cai, J.C. He, L. Zhu, X. Chen, F. Zheng, G.E. Striker, et al., Oral glycotoxins determine the effects of calorie restriction on oxidant stress, age-related diseases, and lifespan, Am. J. Pathol. 173 (2) (2008) 327–336.
[118] J. Uribarri, S. Woodruff, S. Goodman, W. Cai, X. Chen, R. Pyzik, et al., Advanced glycation end products in foods and a practical guide to their reduction in the diet, J. Am. Diet. Assoc. 110 (6) (2010), pp. 911–6. e12.