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REVIEW

Advanced Glycation End Products and Health: A Systematic Review

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Abstract
Advanced glycation end products (AGEs) have garnered significant attention due to their association with chronic diseases and the aging process. The prevalence of geriatric diseases among young individuals has witnessed a notable surge in recent years, potentially attributed to the accelerated pace of modern life. The accumulation of AGEs is primarily attributed to their inherent difficulty in metabolism, which makes them promising biomarkers for chronic disease detection. This review aims to provide a comprehensive overview of the recent advancements and findings in AGE research. The discussion is divided into two main sections: endogenous AGEs (formed within the body) and exogenous AGEs (derived from external sources). Various aspects of AGEs are subsequently summarized, including their production pathways, pathogenic mechanisms, and detection methods. Moreover, this review delves into the future research prospects concerning AGEs. Overall, this comprehensive review underscores the importance of AGEs in the detection of chronic diseases and provides a thorough understanding of their significance. It emphasizes the necessity for further research endeavors to deepen our comprehension of AGEs and their implications for human health.

Keywords AGEs · Glycation · Diabetes complications · Pathological mechanisms · Detection methods

Introduction

AGEs encompass a group of compounds that arise from non-enzymatic reactions between the carbonyl group of reducing sugars and the free amino groups found in proteins, lipids, or nucleic acids. These compounds can be acquired through dietary intake or synthesized endogenously within the organism [1].

AGEs can be generated through diverse chemical pathways, of which the Maillard reaction stands out as the most extensively investigated non-enzymatic process. This reaction involves the addition of terminal amino groups derived from macromolecules (such as amino acids, proteins, and nucleic acids) to the carbonyl groups of reducing sugars (such as glucose, pentose, and xylose) under non-enzymatic conditions [2]. The ensuing reversible Schiff bases undergo Amadori rearrangement, leading to the formation of stable aldehyde amines, which are commonly known as the Maillard reaction products. This sequence of reactions culminates in the generation of glycation molecules termed Amadori products or early glycation products. Subsequent rearrangements, oxidation, reduction, dehydration, condensation, fragmentation, and cyclization of Amadori products facilitate the production of irreversible AGEs [3].

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Specifically, the formation of Amadori products serves as a key step in this process, as they progress through various chemical transformations (Fig. 1) to ultimately generate irreversible AGEs. AGEs have been implicated in the pathogenesis of numerous diseases, making the understanding of their formation and underlying mechanisms a topic of great interest in the field of medical research.

AGES in Food

In addition to endogenous AGEs, high-heat processed and fried foods that are rich in fat and protein constitute the primary sources of exogenous AGEs [4]. The application of high-temperature processing to modify the flavor and color of foods is a prevalent cooking method in modern diets (e.g., roasted coffee, cocoa and cereals, baked cakes and breads, and roasted meats) [5]. These desired attributes are attributed to the Maillard reaction, which involves the reaction of carbonyl groups of reducing sugars with free amino groups of proteins. However, along with achieving the desired seasoning and coloring, the formation of carboxymethyllysine (CML), carboxyethyllysine (CEL), and other AGEs also occurs [6].

Since the proposal of AGEs by Maillard in 1912, their endogenous and exogenous sources have been recognized. Extensive experimental work and studies have been conducted to analyze AGE contents in various foods. In 2004, the CML content of 250 foods was assessed using the ELISA (CML only) method [7]. Subsequently, in 2010, the CML database was expanded to accommodate 549 foods [8], and in 2012, 257 foods were detected utilizing the ultra performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) method, capable of detecting CEL and Methylglyoxal-derived hydroimidazolone 1(MG-H1) based on CML [6]. Numerous research studies have been carried out on the identification of specific AGEs. For example, investigations have delved into the lysine content in milk, revealing a range of approximately 6.7 to 190 μg/mg [9]. Similarly, the concentration of MG-H1 in peanuts has been reported to vary from 0 to 14.75 μmol/L [10].

AGEs and Health

How AGEs Affect Health

Due to the intricate and diverse nature of in vivo AGE formation, the complete characterization of cross-linked AGE structures remains elusive. Certain studies have categorized specific AGEs as toxic, such as CML, CEL, and pyridine, whereas others are considered non-toxic, typically originating from glyceraldehyde or glycolaldehyde [11]. However, as research progresses, it has been discovered that certain non-cross-linked AGEs (traditionally considered non-toxic), including CML [12], indirectly contribute to pathological endothelial cell dysfunction and macrophage apoptosis [13]. AGEs play a significant role in the development and progression of various diseases, including diabetes, chronic kidney disease, tumors, memory loss, eye disorders, polycystic ovary syndrome, cardiovascular complications, bone-related ailments, periodontitis, and erectile dysfunction [14]. The pathogenic pathways attributed to AGEs primarily involve two aspects: firstly, AGEs crosslink with macromolecular substances such as proteins or nucleic acids, leading to structural and functional impairments and even tissue damage; secondly, AGEs bind to specific receptors and subsequently induce tissue destruction by indirectly modifying cellular

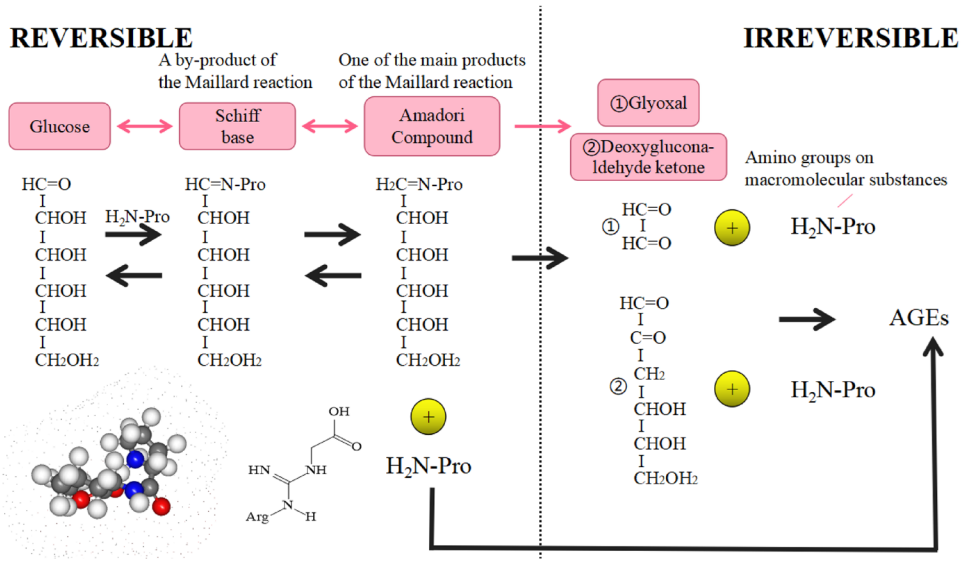

Fig. 1 The chemical process of glucose formation of AGEs through the Maillard reaction. The lower left corner shows the common molecular structure of H_2N-Pro and its 3D model

structure and function, for instance, by promoting inflammation (Fig. 2) [15]. This dual mechanism underscores the multifaceted impact of AGEs on cellular and tissue homeostasis, contributing to the progression of various chronic diseases.

Upon binding with proteins, AGEs form highly stable protein cross-links, leading to structural and functional alterations in the proteins. This modification disrupts cellular signaling, membrane integrity, and enzymatic activities, thereby impacting normal cellular functions. Additionally, AGEs promote oxidative stress, stimulate immune cells to release inflammatory cytokines, and induce cell apoptosis, all of which contribute to the disruption of normal cellular and tissue functions.

Furthermore, AGEs enhance cellular adhesion and migration, activate inflammatory responses by interacting with the extracellular matrix, and trigger the release of cytokines and chemokines, thereby facilitating the invasion and metastasis of tumor cells. AGEs also stimulate endothelial cells to secrete vascular growth factors, promoting angiogenesis and providing increased oxygen and nutrients to tumor cells. Moreover, AGEs suppress the activity of immune cells, diminishing their capacity to target tumor cells.

In conclusion, the multifaceted impact of AGEs on cellular and tissue functions, as well as their complex role in cancer progression, necessitates further research to comprehensively elucidate the underlying mechanisms. Such understanding is crucial for the development of effective strategies aimed at preventing or treating AGE-related diseases.

Exogenous AGEs

AGEs are formed endogenously in the human body, raising concerns about the potential harm they may cause and the impact of exogenous AGE consumption on their levels. Semba et al. observed the presence of AGEs in urine [16], while Courten et al. reported that 30% of urinary AGEs were detected in healthy individuals after oral intake, suggesting an absorption rate of 10% for exogenous AGEs [17].

Toshiyuki et al. conducted a study revealing that approximately 6–7% of dietary AGEs accumulate in the body [18]. Similarly, Sneson et al. found that only 10–30% of orally administered AGEs are absorbed into the systemic circulation in normal subjects [19]. Notably, investigations on mice fed low- and high-CML diets showed significant findings regarding fecal and urine excretion rates. Fecal excretion accounted for 31.7% of ingested food on the low-CML diet and 22.5% on the high-CML diet, while urine excretion rates were 24% and 15%, respectively. These results demonstrate that a considerable portion of CML, up to 56%, is eliminated through urine and feces after consumption. However, it is worth mentioning that a higher CML diet leads to a reduced

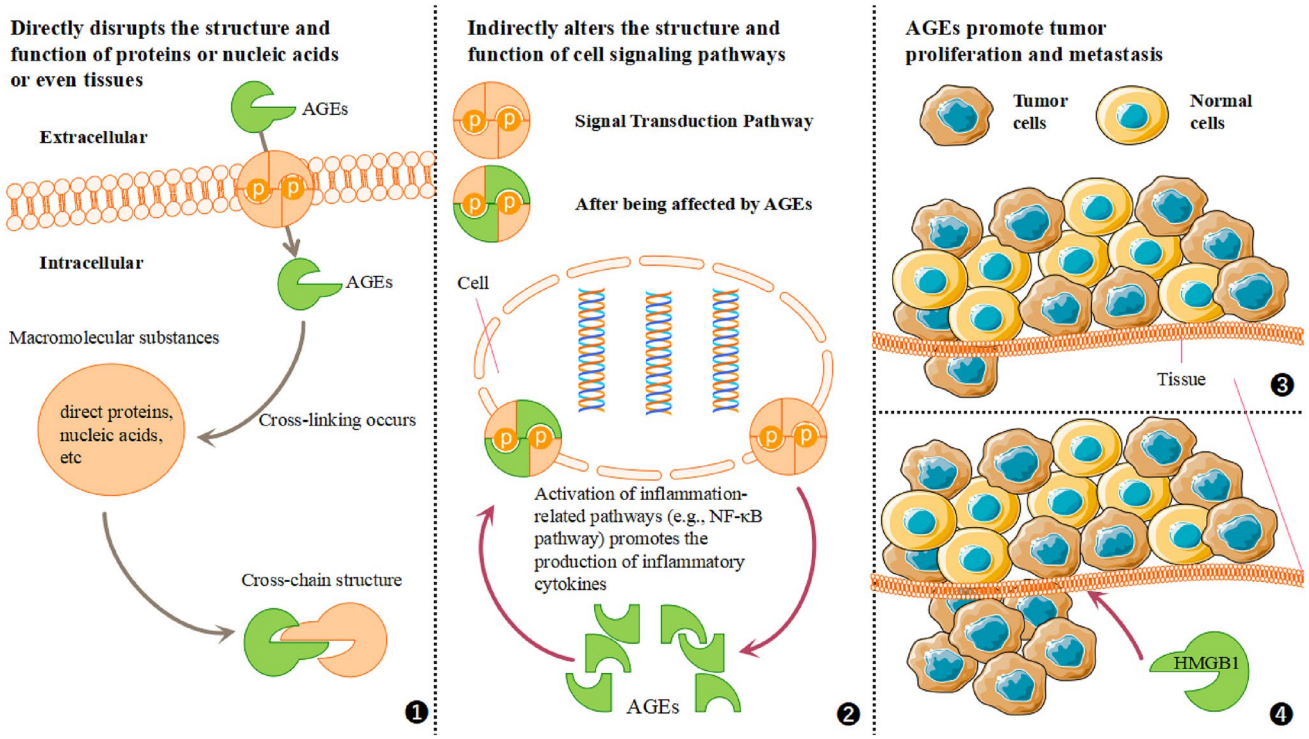

Fig. 2 Effects of AGEs on human body and tissues: direct and indirect impacts (1 and 2); comparative analysis of AGEs (HMGB1) effects on tumor cell proliferation and metastasis (3 and 4)

rate of CML excretion in both stool and urine compared to a lower CML diet [20].

In CKD patients, Šebeková et al. found a positive correlation between dietary AGE intake and serum CML levels [21], a view confirmed by Uribarr et al. [22]. Most studies have shown that restricting dietary AGEs can improve primary and secondary health outcomes in humans. Due to limitations in obtaining human tissue samples for clinical trials, research investigating the relationship between dietary AGEs and AGE accumulation has primarily focused on rodents. Animal studies indicate that restricting AGE intake to at least half of the original amount can help control HOMA-IR (homeostatic model assessment of insulin resistance) [23], tumor necrosis factor-alpha (TNFα) [24], and adiponectin levels in patients with type 2 diabetes mellitus (T2DM) [25], as well as reduce total cholesterol levels over time [26].

AGEs play a prominent role in chronic diseases among older individuals through direct or indirect harm to the human body. They increase oxidative stress and inflammation [27], leading to related chronic diseases caused by inflammation and oxidative stress [28]. Consequently, understanding the relationship between endogenous and exogenous AGEs and aging is crucial. With age, AGE accumulation in the body increases, physical functions decline, and AGE metabolism slows down, making exogenous AGEs the primary source of AGEs in the body [29].

In conclusion, the absorption of identical AGEs consumed by young children and the elderly varies significantly. Individuals with a high accumulation of AGEs in their bodies, such as diabetic patients, have impaired AGE metabolism, resulting in continued AGE accumulation and a detrimental cycle. Therefore, proactive regulation of dietary AGE consumption is essential to mitigate the risk of chronic diseases. Adjusting our diet as we age by reducing AGE intake can effectively contribute to maintaining good health.

Emerging research has provided compelling evidence regarding the direct and indirect role of AGEs in the onset of chronic illnesses. Furthermore, it has been observed that the accumulation of AGEs in the body is positively correlated with the likelihood of developing chronic conditions as individuals advance in age. The existence of regional disparities in disease prevalence and longevity further highlights the influence of dietary habits on differential AGE accumulation, subsequently contributing to specific chronic ailments. Therefore, a thorough investigation into the intricacies of AGEs is crucial to comprehend their precise relationship with various diseases, including AGEs in the onset of chronic illnesses (Table 1) [30–39]. By mitigating the impact of AGEs on cellular and tissue function, independent of enhancing AGE metabolism, it may be possible to effectively manage regional chronic diseases and improve overall health outcomes.

Table 1 Impact of AGEs on disease

Study	Mechanism of action	Disease
Omolaoye et al. [30]	Reactive Oxygen Species (ROS) Malondialdehyde (MDA) GO (CML precursor)	Male infertility
Wang et al. [31]	Affects glucose and lipid metabolism	Diabetic complications atherosclerosis
Mengstie et al. [32]	Induces retinopathy, nephropathy, neuropathy, atherosclerosis	Diabetes
Eguchi et al. [33]	Affects skeletal muscle index (SMI)\bone mineral density (BMD)	Sarcopenia
Snelson et al. [34]	Affects intestinal barrier integrity Accelerated changes in the gut microbiota during disease development	Intestinal diseases
Rojas et al. [35]	Increase tumor progression in solid malignant tumors Promotes RAGE absorption	Tumors gallbladder cancer
Malik et al. [36]	Protein carbonylation Glutathionylation	Oxidative inflammatory stress
Lee et al. [37]	ROS Cross-links with matrix proteins	Microvascular/macrovascular complications
Reynaert et al. [38]	Chronic inflammation	Chronic obstructive pulmonary disease (COPD) Diabetes Cardiovascular diseases Osteoporosis Sarcopenia Renal disease Depression and anxiety
Faruqui et al. [39]	Immunotherapy Carbonyl stress Anti-RAGE therapeutics	Cancer

Detection

The four most widely used methods for adjunctive medical testing of AGEs are high-performance liquid chromatography (HPLC), mass spectrometry (LC-MS/MS), gas chromatography (GC), and enzyme-linked immunosorbent assay (ELISA) [40–43]. The selection of these methods depends on the specific detection needs and sample conditions. Fluorimetric method is used for detecting fluorescent AGEs in serum, urine, and saliva. Although it is simple and fast, it cannot detect non-fluorescent AGEs [44] and is susceptible to interference by non-AGE fluorescent substances. Autofluorescence spectroscopy has been proposed as an alternative for non-invasive detection through the skin [45], but it is affected by skin tone [46].

HPLC is a less invasive and suitable method for long-term monitoring of CML, CEL, Methylglyoxal (MG) in plasma and tissue, but it is time-consuming and can only detect AGEs with known structures [47]. GC-MS and LC-MS/MS are mature technologies with high sensitivity but require complex operations and expensive consumables [48, 49]. UHPLC is faster than GC-MS and LC-MS/MS [50]. ELISA is a simple, fast, and inexpensive method commonly used for detecting AGEs in serum, urine, and tissue [51], but it is susceptible to interference [52]. Western blotting is an ultra-specific method targeting AGEs with a precise chemical formula [53, 54], but the detection process is complex and the accuracy is not high enough.

AGEs can also be detected using fluorescence-based methods, which offer distinct advantages for non-invasive testing on the ocular surface, overcoming the limitations of skin color differences [55]. Compared with traditional detection techniques like mass spectrometry and chromatography, fluorescence-based methods require fewer sample preparation steps and demonstrate higher sensitivity. In addition, a wide variety of fluorescent probes are available to detect diverse AGE compounds.

An important recent development in this field is the application of autofluorescence, which makes use of the intrinsic fluorescence properties of tissue without requiring exogenous fluorescent markers. This approach significantly enhances the safety of non-invasive AGE detection within the human body. These fluorescence-based techniques have already been successfully employed in the analysis of real-world samples, including serum and tissue specimens [55].

However, two significant challenges exist in AGE research. Firstly, the complex structure and mode of operation of many AGEs make direct observation difficult. Secondly, creating a personalized database of AGEs is challenging due to variations in individual body mechanisms. AGE accumulation is associated with related diseases, but the exact relationships between them are unclear, hindering disease control and treatment.

In summary, high-sensitivity methods are suitable for physical medical treatments, whereas methods that require numerous sample studies must consider the cost of consumables. Each method has its own advantages and disadvantages, and the selection of the most appropriate approach depends on the research objectives. The complex structure and mode of operation of many AGEs make direct observation difficult (Fig. 3), posing challenges for their comprehensive investigation. Further research into AGEs is required to address these challenges and create a personalized database for a more complete understanding of their effects on health outcomes.

Advancements in Research and Current Trends

Chronic diseases, such as diabetes, have garnered increasing attention in recent years due to their significant impact on public health. In 2019 alone, diabetes was responsible for 1.5 million deaths worldwide, according to the World Health Organization. Balancing good health and quality of life presents a major challenge in the field of chronic disease management. AGEs have emerged as a critical area of study in this field given their continuous direct and indirect effects on the body. Relying solely on self-perception of one's physical state may result in delayed medical attention. While there remain obstacles in AGE research, their connection to chronic diseases has been preliminarily studied and can serve as adjunctive medicine [56].

In 2019, Yawara Eguchi et al. aimed to determine whether AGEs, as indicated by skin autofluorescence (SAF), serum and urinary pentosidine levels, and serum homocysteine levels, could serve as biomarkers of myopenia in older women. The study tested 70 elderly women, and the findings showed that among the biomarkers of aging, serum pentosyl is associated with a reduction in thin appendix mass and can serve as a biomarker for sarcopenia. Additionally, SAF and homocysteine values were positively correlated and correlated with age [33].

Also in 2019, Ramin Ghodsi et al. conducted a randomized double-blind, placebo-controlled clinical trial in 36 autistic children who received 500 mg of carnosine supplementation or placebo daily for two months. The study measured plasma concentrations of glycosylation and lipid oxidation marker precursors via enzyme-linked immunosorbent assay. The findings indicate that carnosine supplementation did not change AGEs and precursor of advanced lipoxidation end products in autistic children [57]. Ami Sotokawauchi et al. aimed to determine whether fructose can cause endothelial cell damage through activation of AGE-RAGE. The study evaluated intracellular AGEs via dot blot analysis and prepared fructose-derived AGEs (Fruc-AGEs) by

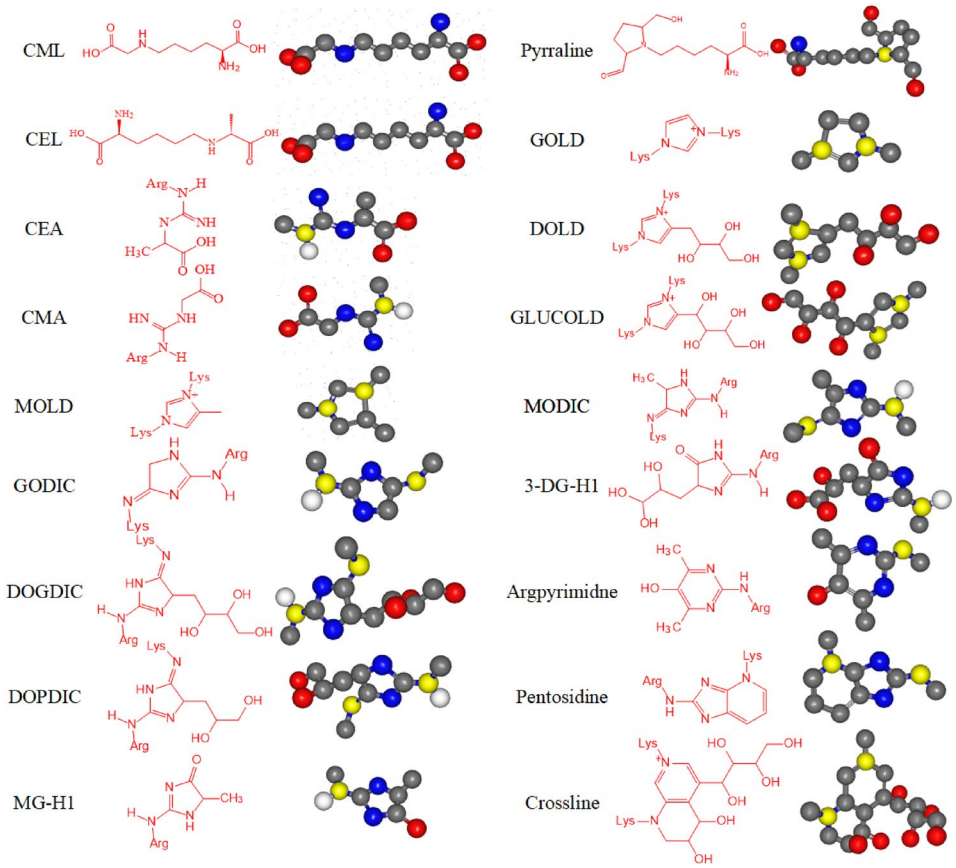

Fig. 3 Eighteen common AGEs. Non-carbon atoms are depicted in gray, unoxygenated atoms in red, and hydrogen atoms (For better observation, the attached part of the carbon atom is omitted) in white. The blue color represents a N atom, while yellow is used to indicate N atoms or N + ions attached to lysine (Lys) or arginine (ARGs). The combination of yellow and gray denotes the presence of N + ions, while the combination of yellow and blue signifies the presence of N

incubating bovine serum albumin with fructose for 8 weeks. The findings indicate that fructose increased the advanced glycation end-product-specific fluorescence intensity in assay medium while stimulating intracellular formation of AGEs. They speculate that fructose may cause endothelial cell damage by activating the AGE-RAGE axis [58].

In 2020, Takashi Nishinaka et al. compared the effect of a single sulfated polysaccharide on toxic AGE uptake by mouse cells. The study treated cells simultaneously with each sulfated polysaccharide and fluorescently labeled BSA, AGE−2, or AGE−3 (200 μg/mL) and determined their fluorescence intensity by flow cytometry analysis. The findings indicate that fucoidan and carrageenan, but not the other sulfated polysaccharides examined, had inhibitory activities on toxic advanced glycation end-product uptake and toxic advanced glycation end-product-induced upregulation of scavenger receptor-1 class A, possibly due to structural differences among sulfated polysaccharides. They believe that fucoidan may be useful for treatment and prevention of AGE-related diseases [59].

Also in 2020, Hawa Edriss et al. found that patients with acute respiratory failure often had high blood sugar, which can cause acute lung injury by producing AGEs. The study recorded glucose, advanced glycation end product, glycated albumin, circulating glycated hemoglobin, and soluble advanced glycosylated end-product receptor (sRAGE) levels at admission, 24 h, and 72 h in 40 patients with acute respiratory failure requiring mechanical ventilation. The results suggest that there is no consistent change in sRAGE levels in patients with acute respiratory failure requiring mechanical ventilation [60].

In 2021, Akiko Kobori et al. conducted a study to determine the impact of AGEs on the cognitive function of patients diagnosed with schizophrenia. This study assessed neuropsychological and cognitive function in 58 patients diagnosed with chronic schizophrenia. Plasma levels of advanced glycation end products (AGEs) were measured via high-performance liquid chromatography (HPLC). Cognitive assessments were conducted using the Wechsler Adult Intelligence Scale Third Edition and the Wisconsin Card Classification Test Keio-FS Edition to provide a comprehensive evaluation of cognitive function. The findings suggest that AGE-reducing therapy may be effective in improving processing speed in patients with schizophrenia, and they hope that interventions for AGEs, such as administration of vitamin B6 or modifications of adverse lifestyles, will be useful treatment options to improve patient recovery and cognitive function [61].

Also in 2021, Lee Jinyong et al. established a convenient and accurate in situ measurement system for facial glycation

end products by investigating the correlation between skin glycation index and facial skin elasticity and age in 36 healthy Korean women. This system can facilitate accurate monitoring of skin glycation index in situ, which is valuable for skin aging research, such as anti-glycation cosmetics research [62].

Mitsuhiro Miyashita et al. selected 277 13-year-old community adolescents who were not receiving antipsychotic medication for twelve months of follow-up by fingertip AGE assay (FAF reader (Sharp Life Science Corporation (Japan)) and experienced psychiatrists. Thirteen of them (4.7%) had persistent psychotic symptoms, 65 (23.5%) had transient psychotic symptoms, and 199 (71.8%) had no psychotic symptoms. The findings suggest that AGEs may predict the trajectory of psychotic symptoms in non-drug adolescents [63].

In 2022, Yao-Chang Chen et al. investigated the electrical activity and Ca2 + homeostasis or signaling of isolated right ventricular outflow tract myocytes with or without advanced glycosylation end products (100 μg/mL) by whole-cell patch-clamp, routine electrophysiological studies, fluorescence imaging, western blotting, and confocal microscopy. The findings indicate that AGEs modulate right ventricular outflow tract electrophysiological characteristics with larger late sodium current, intracellular Na + , reverse mode Na + –Ca2 + exchanger currents, and disturbed Ca 2 + homeostasis through increased oxidative stress mediated by the activation of the AGE signaling pathway [64].

Also in 2022, Wenbo Mao et al. confirmed the anti-EndMT effect of phlorytin in a diabetes model, discovering a compound that potentially alleviates vascular complications of diabetes [65].

Recent research has demonstrated that the binding of AGEs to proteins results in the formation of highly stable protein cross-linkers, profoundly altering protein conformation and functionality. This protein cross-linking exerts effects on diverse cellular processes such as signaling, membrane permeability, and enzymatic activity. AGEs also contribute to the initiation of oxidative stress, leading to detrimental outcomes like lipid peroxidation and DNA damage. These oxidative insults are closely associated with the development of various diseases, including cancer and atherosclerosis. Moreover, AGEs prompt immune cells to release inflammatory mediators, subsequently eliciting an inflammatory response. Prolonged inflammation can induce tissue impairment and disease progression. Additionally, AGEs possess the ability to induce apoptosis, resulting in tissue and organ damage, which further exacerbates disease pathogenesis. Significant discoveries on AGEs from recent research (Table 2) [66–87] shed light on these crucial mechanisms and their implications for health and disease.

Furthermore, AGEs facilitate cell adhesion and migration to the extracellular matrix, thereby promoting tumor cell invasion and metastasis. AGEs also stimulate vascular endothelial cells to secrete angiogenic factors, fostering neovascularization and enhancing oxygen and nutrient supply to tumor cells. In addition, AGEs inhibit immune cell activity, thus diminishing their capacity to combat tumor cells. By activating inflammatory responses and triggering the release of cytokines and chemokines, AGEs contribute to the invasion and metastasis of tumor cells.

In conclusion, AGEs have a profound impact on protein structure and function in various domains, leading to the initiation and progression of multiple diseases through the induction of oxidative stress, inflammatory responses, and cellular apoptosis. However, further investigation is warranted to fully comprehend the underlying mechanisms by which AGEs contribute to disease pathogenesis. These insights hold the potential to inform the development of targeted therapeutic interventions that specifically target the RAGE signaling axis. By leveraging this research, there is a possibility to effectively manage regional chronic diseases and enhance overall health outcomes.

Conclusions

Overall, this review contends that methodological investigations into the detection of AGEs overly rely on invasive techniques and insufficiently utilize fluorescence-based approaches. Currently, conducting research on localized diseases related to AGEs poses considerable challenges, and there exists a limited comprehension of AGEs among the general population. Drawing upon recent research and critical analysis, this article underscores several pivotal aspects:

- AGEs have been demonstrated to play a significant role in the pathogenesis and progression of various chronic diseases, such as diabetes, cardiovascular diseases, and neurodegenerative disorders.
- It is crucial to emphasize the significance of dietary intervention in mitigating the impact of excessive AGE intake. Repeated consumption of substantial quantities of AGEs can instigate a detrimental cycle, wherein AGEs accumulate, impede metabolism, and eventually contribute to an irreversible feedback loop. Analogous to the incurable nature of diabetes in its advanced stages, heightened awareness regarding the implications of AGEs is imperative for individuals afflicted with localized chronic diseases. Moreover, additional researchers are warranted to pinpoint specific issues pertaining to individuals' dietary habits and curtail the prevalence of regional diseases at their core.
- Research on AGEs is still relatively limited. However, it would be reasonable to establish a risk threshold in the annual physical examination, which can provide guid-

Table 2 Key findings on AGEs from recent studies

Study	Tested variable	Conclusion
Asgharpour Dil et al. [66]	Medicinal plants	Medicinal plants can be influenced the oxidation of thiol groups in proteins\protein cross-linking\the formation of AMADORI products
Gonzalez et al. [67]	Polyphenols foods	The pathway mediated by antioxidant properties and interference with AGE-RAGE interaction has a protective effect on AGE-induced damage.
Le Bagge et al. [68]	Targeted drugs	Inhibiting binding of ligands to RAGE and the signal transduction pathway induced by RAGE-ligand binding.
Kheirouri et al. [69]	Vitamin D	Inhibition of the activity of positive regulators of RAGE expression by IkappaBalpha(Vitamin D promotes its synthesis) Promoting sRAGE can bind to AGEs and inhibit its binding to membrane RAGE
Olaoba et al. [70]	S100 proteins	RAGE signaling is an important contributor to the proliferative, inflammatory, and invasive phenotypes of melanoma tumors
Qiu et al. [71]	HSA (human serum albumin)	Affects diabetic complications by influencing glycosylation
van Dongen et al. [72]	Endogenous\exogenous AGEs	AGEs causes disease by inducing some changes in the intestines
Rojas et al. [73]	HMGB1 S100 Proteins	HMGB1 promotes the proliferation and metastasis of tumor cells S100 Proteins can reduce the impact of AGEs
Bras et al. [74]	Targeted glycosylation	It is hypothesized that the development of therapeutic strategies targeting glycosylation could serve as an orthogonal approach to the treatment of diabetic complications and neurodegenerative diseases such as HD
Rojas et al. [75]	RAGE	Targeting protein–protein interactions is the most promising method to inhibit RAGE signaling
Drenth et al. [76]	Inflammation	The inflammatory process of AGEs may be a factor in the pathogenesis of a form of dystonia in motion rigidity in patients with dementia
Kitamura et al. [77]	Diet	Diet to reduce the amount of AGE/ALE in the body
Taneja et al. [78]	Tumor cell	RAGE and its ligands stimulate tumor cell survival and promote metastasis under hypoxic conditions
Rojas et al. [79]	Soluble ACE2	Soluble ACE2 can inhibit RAGE axis activation, especially by avoiding transactivation of the RAGE axis caused by virus-mediated imbalance in the ACE/AngII/AT1R pathway
Dozio et al. [80]	Glycosylation	Glycosylation and O-linked-N-acetylglucosamine as glucose-related pathogenic agents and disease markers in cardiovascular remodeling
Singh et al. [81]	Nutrition and AGE/RAGE	Controlling the intake of AGEs while ensuring nutrition can effectively treat diabetic complications
Rojas et al. [82]	RAGE axis	Activated RAGE axes promote tumor growth and spread
Papachristou et al. [83]	AGE detection	The detection of AGEs can be used as a way for patients with urine diseases to assess their own diabetes status
Zawada et al. [84]	Prepared foods	The reheating of prepared foods can produce the formation of a large number of harmful AGEs.
Smith et al. [85]	Diet	High sugar, protein dehydration, high-temperature sterilization to extend shelf life, frying, and microwave heating (and reheating) can lead to very high dAGE levels Dietary modification and lifestyle interventions have the potential to reduce the formation of AGEs, mitigate their oxidation, and reduce the expression of RAGE-receptors
Pinto et al. [86]	AGEs	AGEs can be used as biomarkers of CVD
Delrue et al. [87]	sRAGE	sRAGE can be a biomarker, but it needs to be analyzed for different sRAGE isoforms and co-analyzed with the drug being used.

ance to the patient. In addition, by assessing the rate at which AGEs accumulate in an individual's body, it is possible to assess their dietary status and provide relevant recommendations for individuals who exhibit a higher growth rate.

In conclusion, research on AGEs holds significant importance for both complementary medicine and proactive healthcare. The advancements in dietary interventions, disease prevention, minimally invasive detection techniques, and non-invasive methods have greatly propelled scientific investigations in this field. The prevention and monitoring of chronic diseases are pivotal for the future well-being of individuals, and AGEs have demonstrated undeniable potential in contributing to these efforts.

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Data Availability Not applicable.

Declarations

Competing interests The authors declare no conflict of interest.

Ethical Approval Not applicable.

Informed Consent Not applicable.

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