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RESEARCH ARTICLE

Reducing dietary advanced glycation end products to slow progression of cognitive decline and Alzheimer's disease

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Abstract

Reduction of dietary advanced glycation end product (AGE) consumption could represent a non-pharmacological treatment to improve cognition. Reducing intake of dietary AGEs is associated with better cognitive scores in many studies. Higher intake of dietary AGEs is closely linked to increased risk and faster progression of Alzheimer's disease (AD). When AGEs modify amyloid-β, this increases the amount of amyloid-β accumulation in the brain and worsens memory impairment. Higher dietary levels of AGEs increased the neuronal toxicity of amyloid-β and increased protease resistance in senile plaque. Higher AGE levels also increased the aberrant phosphorylation of tau into neurofibrillary tangles (NFT). Both AGEs and amyloid-β can activate the receptor for AGEs (RAGE). When RAGE is triggered by AGEs, this can increase the expression of nuclear factor kappa-B (NF-κB), creating a cascade of inflammatory cytokines and increasing levels of C-reactive protein. The resulting increased oxidation can contribute to neuronal cell death, lower brain volume, and can increase neurodegeneration. AGEs can modify low-density lipoproteins (LDL), promoting endothelial dysfunction and atherosclerosis, leading to the reduced brain perfusion that was found after meals high in AGEs. Reduction of dietary AGEs may represent a powerful tool to slow cognitive decline and reduce the progression of AD.

Keywords: *advanced glycation end products; mild cognitive impairment; dementia; Alzheimer's disease; amyloid-beta; neuroinflammation; neurodegeneration; oxidation; diet; cognitive decline; receptor for advanced glycation end products; endothelial dysfunction.*

Introduction

Certain foods, mainly animal-derived food, when cooked at high heat, contain high levels of AGEs. It has been proposed that AGEs can contribute to the onset and progression of neurodegenerative diseases. So, if these foods are avoided or instead cooked with moist heat, AGE intake can be greatly reduced, leading to an improvement of cognition [1]. Reducing dietary AGEs can represent an additional tool to reduce risk of and progression of neurodegenerative diseases, such as cognitive impairment and dementia.

Lower dietary AGEs are associated with better cognitive scores in many studies [2], and may reduce incidence and progression of AD [3]. In AD, AGE-modified amyloid-β can impair memory and increase tau hyperphosphorylation [4]. Reducing dietary AGEs could reduce oxidative stress and decrease neuroinflammation. Reducing dietary AGEs can also reduce the risk of atherosclerosis, thus potentially increasing brain perfusion [5].

AGEs are a diverse group of compounds derived from non-enzymatic glycation of free amino groups of proteins or of lipids. AGEs include both advanced glycation end products and advanced lipoxidation end products, both sometimes called glycotoxins. AGEs can be eaten and absorbed from the diet and are also continuously formed in the body under hyperglycemic and/or oxidative stress conditions. Their toxic effects are related to their ability to promote oxidative stress and inflammation [6]. More specifically, upon binding to receptors, AGEs can activate several signaling pathways, including NF-κB, which can result in increased inflammation and oxidative stress [7].

The most abundant AGE is N(6)-carboxymethyllysine (CML). CML has been the most used marker for AGEs in food analysis. Carboxyethyllysine (CEL) is an AGE that, like CML, is formed at the advanced stage of the Maillard reaction and both are found in high levels in cooked meat. Both CML and CEL are measured with mass spectrometry. Methylglyoxal (MG) is involved in the formation of AGEs. MG is an intermediate product of the Maillard reaction that can be derived from food. Methylglyoxal reacts with free amino groups of lysine and arginine and with thiol groups of cysteine to form AGEs. Pentosidine is a biomarker for AGEs and acts as a toxin itself. Pentosidine fluoresces, which allows it to be measured easily. Tissue AGE accumulation can be estimated using the relatively simple, noninvasive measurement of skin autofluorescence. Crossline is a fluorescent AGE. Pyrraline is an AGE almost exclusively of dietary origin [8]. Hydroimidazolone is a MG-derived AGE that could contribute to atherosclerosis via modification of LDL, increasing macrophage and foam cell formation [9].

AGEs and cognition

Advanced glycation end products increase oxidative stress, inflammation, and neurotoxicity. Dietary AGE load can be easily and safely reduced by eating less animal-derived food or by using food processing methods that limit high or prolonged heat application and that preserve food moisture.

Slowing cognitive decline

In humans, a reduced intake of food-derived AGEs has been considered an effective strategy to reduce risk of neurodegenerative diseases, and an association has been shown between high serum AGEs and cognitive decline [10]. Many studies have reported that lower levels of serum AGEs are associated with a slower rate of cognitive decline [11]. In a group of cognitively intact subjects, at least 75 years old, those with lower serum levels of MG showed a reduced rate of cognitive decline [12]. Among 4041 elderly Japanese, the highest AGE levels were associated with the lowest cognitive scores, while the lowest levels of AGEs were associated with the highest cognitive scores [13].

When AGE levels rose to half of the maximum AGE levels measured in healthy people, the risk of mild cognitive impairment

(MCI) rose 640% (OR=6.402), and this was after adjustment for age and brain atrophy measured by magnetic resonance imaging (MRI). Also, both brain atrophy and AGE content were significantly higher in patients with MCI [14]. In the prospective Rotterdam Study, higher levels of AGEs were associated with lower global cognitive function and this effect was stronger for carriers of the APOEε4 allele. Lower AGEs measured by skin autofluorescence were associated with better cognition in 2890 individuals in a Dutch study [15].

A recent study found that, after 4 years, higher AGEs were found to be significantly associated with a worse clinical dementia rating. This difference in clinical dementia rating remained significant after adjustment for age, sex, education level, and apolipoprotein E4 status. This study indicates that a high concentration of AGEs may be a predictor of long-term decline in cognition-related daily living performance in patients with AD. Importantly, those patients with lower AGEs were slower to decline in cognition [16].

CML was increased in the cerebrospinal fluid of subjects with Alzheimer's disease. The decline in cognitive function in AD subjects was linked to protein glycation by MG [17]. Higher levels of AGEs measured by skin autofluorescence are associated not only with an increased risk of dementia, but also with lower brain volumes. Each standard deviation increase of AGEs increased AD and dementia risk 21-22%. With APOE ε4 carriers, risk of dementia increased 38% and risk of AD increased 51% for each standard deviation. For every one standard deviation of increase in AGEs, total brain volume was decreased (-2.71 mL) on MRI, and grey matter volumes decreased (-1.77 mL) [18].

MG and AGEs in cognitive decline

MG, which represents a modifiable risk factor for AD, amplifies the proinflammatory properties of amyloid-β and NFTs. High MG levels in the brain or the circulation are linked to cognitive decline in elderly subjects [19]. One observational clinical study correlated increased serum levels of AGEs with memory decline in humans. Their results suggest that a low-AGE diet may reduce the risk of AD [20].

One study measured the relationship between MG derivatives in the blood and cognitive decline in 267 non-demented elderly participants. Lower levels of baseline serum MG were associated with a slower rate of cognitive decline, even after adjusting for several sociodemographic and clinical characteristics. MG can impair glucose metabolism and lead to energy depletion in neuronal cells. AGE concentrations in the cerebrospinal fluid of AD patients were approximately double that of controls in two studies [21].

In a study with 378 participants, mean age 72.1 years, MG was associated with poorer memory and executive function. Grey matter volume was also reduced in those with higher MG. Higher baseline urinary pentosidine levels predicted greater decline in cognitive speed over 9 years. The levels of AGE accumulation in cortical neurons and cerebral vessels correlated with the severity of cognitive impairment [22].

Higher levels of circulating MG were associated with a faster rate of cognitive decline, after adjusting for several sociodemographic and clinical characteristics. Since levels of MG in blood correlate with AGEs consumed in the diet, lowering MG by an AGE-restricted diet could potentially slow cognitive decline [23].

AGEs, cognitive decline and vascular dementia

Carboxymethyllysine (CML) is the AGE that accumulates the most in vascular tissue and atherosclerotic lesions. Increased accumulation of CML is being viewed as potentially causative in vascular dementia [24]. Cognitive dysfunction in vascular dementia may relate to microvascular disease, which may be increased by the accumulation of AGEs. Among people with cerebrovascular disease, those with dementia have higher levels of neuronal and vascular AGEs. Cognitive function was inversely associated with neuronal and vascular AGE levels [25]. The increased accumulation of AGEs in brains of AD patients may increase vascular damage due to glycation and oxidative stress [26].

Tissue levels of CML in cortical neurons and cerebral vessels were related to the severity of cognitive impairment in patients with cerebrovascular disease. It has been demonstrated that MG is involved in the increased levels of AGEs observed in AD [27]. MG reacts relatively rapidly with proteins to form AGEs; MG is up to 20,000 times more reactive than glucose in glycation reactions. The insolubility and protease resistance of amyloid-β plaques are caused by extensive AGE-covalent protein cross-linking. Amyloid-β plaque from AD brains contained about 3-fold more AGE adducts when compared to non-AD brains [28].

AGEs and brain pathology

Studies that assessed cognition in elderly individuals strongly suggest that AGEs could contribute to loss of cognition [29]. Strong trends were observed for an association between AGEs and poorer cognitive performance on the digit symbol substitution test, suggesting a potential relationship of AGEs with processing speed and working memory. Higher AGEs also associated with decreased grey matter volume in the brain [30]. A one-year study of 144 people indicated that high AGE levels could be a contributing factor to functional mobility decline in addition to progressive brain pathology [31]. A high level of circulating MG correlates with impaired cognition in humans, suggesting that high levels of dietary AGEs can impair cognitive function [32].

Reduced dietary AGEs and Alzheimer's disease

MG and glycation can contribute to the progression of neurodegeneration [33], and available data suggest that dietary AGEs contribute to AD [34]. AGEs have been found to accumulate in the specific brain regions with advanced pathology (e.g. the hippocampal regions in Alzheimer's disease, substantia nigra in Parkinson's disease, and ventral spinal cord in amyotrophic lateral sclerosis) [35]. AGEs are difficult to break down due to the protease-resistant crosslinks between the AGEs and proteins or lipids [36]. Since significant correlations have been found between high circulating AGEs and impaired cognition in older humans [37], a therapeutic strategy of AGE reduction may offer a new approach to combat the epidemic of AD.

Reduction of AGEs, by reducing meat consumption, can be considered a risk-modifying factor for AD pathology. Lowering the amount of dietary AGEs from the average amount of 15,000KU/day to 7,500KU/day, could be a very realistic target. A dietary AGE reduction of this magnitude has been found to significantly alter the levels of circulating AGEs and at the same time reduce levels of oxidative stress and inflammation markers, which have been linked to neuronal death in AD [38].

Importantly, reduction of dietary AGEs is feasible and may provide an effective non-pharmacological strategy. In older healthy humans with lower baseline circulating MG levels, there was less of a decline in cognition. On the contrary, even after adjusting for factors such as age, sex, education, and baseline mini-mental state examination, high baseline serum MG levels were found to predict a cognitive decline over a period of 9 months. High serum MG, a marker of dietary AGE intake, may be a marker for dementia risk in older adults [39].

Importantly, impaired spatial learning and recognition memory have been reported in older humans with diets high in AGEs, but not in those with diets low in AGEs. So, it can be hypothesized that AGE restriction may improve cognition in humans [40]. Detailed investigations show that altering dietary AGE intake plays an important role in senile dementia [41].

AGE-induced pathological modifications in AD

Neurodegenerative diseases are characterized by the progressive loss of neurons and the deposition of misfolded and/or aggregated

proteins in the brain. Proteins such as amyloid-β and tau can be glycated and the extent of glycation is correlated with the pathologies of the patients. AGE consumption can trigger the abnormal deposition and accumulation of these modified proteins, which in turn increases the local oxidative stress and inflammatory response, eventually leading to the clinical aspects of AD [42].

Amyloid

Many times more AGEs have been found in amyloid-β plaques in AD brains, compared to normal brains [43]. Glycation increases the neuronal toxicity of amyloid-β in hippocampal neurons. AGE-modified amyloid-β decreased cell viability, increased apoptosis, increased tau hyperphosphorylation, and increased damage to nerve synapses. Inhibiting amyloid-β-AGE formation was found to rescue cognitive impairment [44].

When AGEs are detected inside amyloid plaques in AD, the accumulation of AGE-modified amyloid-β in cells and tissues is accelerated [45]. The brains of AD patients typically contain 5- to 10-fold greater numbers of amyloid plaque, compared to age-matched healthy controls [46]. The cross-linking of protein mediated by AGEs can accelerate polymerization of amyloid-β and contribute to amyloidosis in AD [47].

The aggregation and deposition of damaged proteins derived from AGE modification and the resulting cross-linking have been observed in amyloid-β plaques. AGE accumulation has been shown in senile plaques in different cortical areas and in glial cells in the AD brain. The polymerization of amyloid-β, the major component of senile plaque, was shown to be significantly accelerated by AGE-mediated protein cross-linking. AGEs also can trigger the abnormal accumulation and deposition of the AGE-modified amyloid-β by increasing protease resistance and insolubility [48].

AGEs increased the size of amyloid-β deposits. In AD patients, the percentage of AGE-damaged neurons (and AGE-damaged astroglia) increases with the progression of the disease [49]. AGEs extensively cross-link proteins in amyloid-β deposits, making them more toxic. AGE-modified amyloid-β was found to be more toxic than non-glycated amyloid-β to synaptic proteins [50].

The ApoE4 isoform may promote aggregate formation in the AD brain by more readily binding to AGE-modified plaque components, which may partially explain why ApoE4 contributes to an increased risk of AD. The ApoE4 isoform exhibited a 3-fold greater binding activity to AGEs than the ApoE3 isoform [51].

AGE-modified Tau

AGEs contribute to the toxicity of NFTs. Tau protein in AD was glycated and the glycated tau was able to induce oxidative stress. Interestingly, one study reported that AGEs could induce tau protein hyperphosphorylation and impair memory, likely through RAGE activation [52].

When AGEs are detected in NFTs in AD, the accumulation of AGE-modified tau in cells and tissues is accelerated [53]. Moreover, AGE-modified amyloid-β increased tau hyperphosphorylation and increased damage to nerve synapses [54]. The cross-linking of protein mediated by AGEs can induce tau-protein hyperphosphorylation and promote NFT formation [55]. The aggregation and deposition of proteins derived from AGE modification and the resulting cross-linking have been observed in tau tangles. The extent of tau glycation is correlated with localized oxidative stress and inflammatory response in AD [56].

There is a link between AGE accumulation and the formation of NFTs. It has been demonstrated that AGEs are co-localized with NFTs. AGEs extensively cross-link proteins in NFTs [57]. Also, MG induces tau hyperphosphorylation [58].

Amyloid precursor protein

Expression of the amyloid precursor protein was found to be induced by AGEs and RAGE, and the amyloid precursor protein is involved in amyloid-β accumulation in the brain [59]. The excess amyloid precursor protein increased by AGEs could be blocked by the pretreatment of the cells with a reactive oxygen species (ROS) inhibitor (N-acetyl-L-cysteine). These results may help elucidate a new mechanism by which AGEs participate in AD development and reveal another way that AGEs are an important risk factor in the pathogenesis of AD [60,61].

Dietary AGEs and neuroinflammation

Limiting dietary AGE intake may lead to a decrease in inflammation and chronic diseases related to inflammatory status, such as AD. There was a suppression of inflammatory markers in diets with low AGE content, in fact, five studies demonstrated a decrease in circulating concentrations of inflammatory indicators with a low-AGE diet [62].

A sustained reduction in dietary AGEs may result in effective suppression of inflammatory molecules [63]. Dietary restriction of AGEs decreases the concentration of circulating AGEs [64]. AGE restriction reduced inflammation in humans [65].

Consumption of foods rich in AGEs leads to increased production of C-reactive protein and inflammatory cytokines like Tumor necrosis factor-α (TNF-α) [66]. After a dietary reduction of AGEs, a reduction in serum AGE concentrations is accompanied by a simultaneous reduction in markers of inflammation, oxidative stress, and endothelial dysfunction [67]. Conversely, a high-AGE diet increased many inflammatory markers, promoting a sustained inflammatory state. Markers of immune response such as cytokines and adhesion molecules are inducible by AGEs via increased production and activation of NF-κB [68]. On a high AGE diet, the level of TNF-α increased by 86.3%, while it decreased by 20% on a low AGE diet. C-reactive protein increased by 35% on a high AGE diet and decreased by 20% on a low AGE diet (Figure 1) [69].

The interaction of AGEs with RAGE receptors induces the activation of NF-κB and inflammatory mediators like TNF-α, interleukin-6, and C-reactive protein. All of these pathways lead to increased oxidative stress and a proinflammatory status [70].

AGEs and oxidative stress

Oxidative stress is thought to play a causative role in the development of AD [71]. Dietary AGEs are known to contribute to increased oxidative stress [72]. Oxidative stress is important in the initiation and progression of neurodegenerative disorders in that it increases: a progressive decline in neural signal transmission, neuronal loss, and deposition of aggregated proteins in the brain [73].

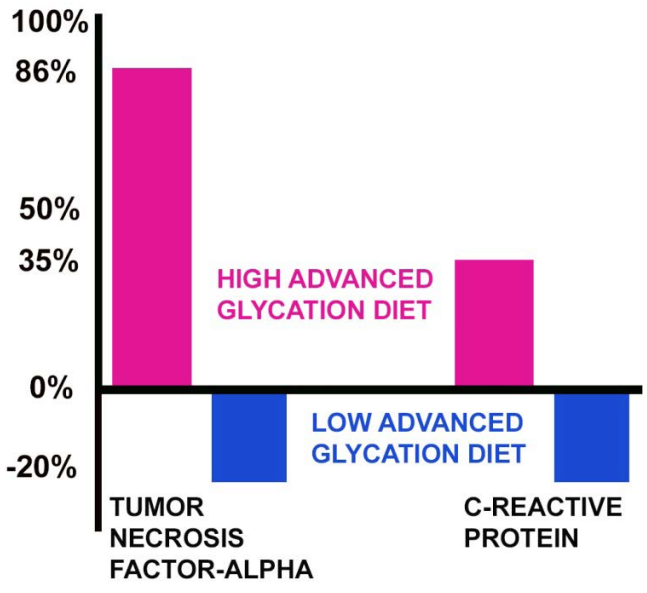

Figure 1: High AGE diets increase two markers of inflammation

In AD, there is an increased presence of AGEs in the brain as well as an increased production of ROS. Oxidative stress was found to increase the expression of RAGE, facilitating amyloid-β accumulation in the brain [74]. Reactions with AGEs may also increase axon damage, inappropriate transmission of neural signals, mitochondrial dysfunction, inflammation, and further oxidative damage. High levels of oxidative stress and inflammation, related to excess AGEs, can lead to neuronal malfunctioning and death [75].

Studies in healthy human beings show that dietary AGEs directly correlate with circulating AGEs, such as CML and MG, as well as with markers of oxidative stress. Importantly, restriction of dietary AGEs reduces markers of oxidative stress and inflammation [76] MG is cytotoxic to cells because of increased oxidative stress and increased induction of apoptosis.

Increasing evidence shows that food-derived AGEs increase the body burden of AGEs, thereby increasing oxidative stress and inflammation [77]. In the body, CML is generated by the oxidative cleavage of Amadori products and CML is an important biological marker of oxidative stress. MG is an intermediate product of the Maillard reaction that can be derived from food. MG is very reactive because it can generate AGEs by modifying lysine or arginine residues of proteins. MG is present at low levels in the circulating blood, but MG has a high specific glycation activity. Therefore, MG is considered as the most reactive glycation agent [78].

MG undergoes auto-oxidation, resulting in ROS generation; these oxidation reactions increase superoxide, hydrogen peroxide, and hydroxyl radical. MG also increases mitochondrial superoxide production. MG is able to reduce the antioxidant power of glutathione [79]. Higher malondialdehyde levels, indicating the oxidation of fats, have been reported in the plasma and serum from AD patients compared to an age-matched control group [80].

Dietary AGEs, atherosclerosis, and reduced brain perfusion

Endothelial dysfunction

Reduced brain perfusion was found after meals high in AGEs, possibly due to significant increases in microvascular endothelial dysfunction. Flow-mediated dilation was used to measure endothelial function by using ultrasound to measure arterial blood flow in the forearm. The meals had identical ingredients but different AGE amounts (15,100 compared with 2,750 kU AGEs). Flow-mediated dilation decreased by 36.2% after the high AGE meal and decreased by 20.9% after the low AGE meal. This impairment of macrovascular function after the high AGE meal was paralleled by an even greater impairment of microvascular function (67.2%), further restricting brain perfusion [81]. The high AGE meal also increased concentrations of serum AGEs and markers of oxidative stress.

AGE crosslinking in endothelial cells leads to endothelial dysfunction that impairs vasodilatation, partially due to decreased production of nitric oxide. Nitric oxide, mainly secreted by endothelial cells, is a potent vasodilator and has marked anti-atherogenic properties. AGE crosslinking in endothelial cells also accelerated macrophage activation to form foam cells. AGE crosslinking in endothelial cells also decreased the flexibility of smooth muscle cells, thus increasing arteriosclerosis. Increased oxidation of LDL was also noted with higher crosslinking of AGEs to endothelial cells [82].

Endothelial dysfunction can precede the onset of atherosclerosis and cardiovascular disease by decades, and is characterized by increased vascular inflammation. Endothelial dysfunction can be worsened by increased AGEs that increase inflammation and oxidative stress. A meal rich in AGEs, but differing from a low-AGE meal only in cooking methods, induced acute endothelial dysfunction. The high AGE meal induced a significant increase in vascular cell adhesion molecule 1 (+19% vs. −5%) and the thiobarbituric acid reactive substances test for oxidation (+23% vs. +6%) [83].

LDL modification

The attachment of AGEs to LDL can lead to the modification of the LDL receptor binding domain. These glycated LDL may then not be recognized by LDL receptors. Glycated LDL become the substrate for macrophages that stimulate foam cell formation and promote atherosclerosis. Macrophage interactions with AGEs can also result in the production of interleukin-1 and TNF-α, which have pivotal roles in the pathogenesis of atherosclerosis [84]. Atherosclerotic lesion severity has shown a close correlation with high AGE diets, with higher levels of circulating AGE-modified LDL, and with higher levels of vascular tissue AGEs [85].

LDL were more glycated and oxidized in subjects fed an AGE-rich diet, compared to subjects fed a lower AGE diet [86]. AGE modification of LDL resulted in reduced LDL plasma clearance, contributing significantly to increased LDL levels. AGEs can increase vascular disease by inducing apoptosis in human endothelial cells, increasing ROS, and stimulating vascular endothelial growth factor over-expression. When AGEs modify hemoglobin and collagen, they have an altered structure that increases their aggregation. AGE-collagen molecules can form crosslinks that contribute to vascular stiffening. Also, AGE-triggered RAGE-mediated ROS production is involved in vascular aging. In addition, those with higher AGEs had a 22% increased risk of lacunar infarcts and a 9% increased risk of microbleeds [87].

RAGE

RAGE (Receptor for advanced glycation end products), found on the cell surface of cerebral vessels, neurons, and microglia, serves as a binding receptor for amyloid-β and AGEs. RAGE mediates amyloid-β transport across the blood–brain barrier and its accumulation in the brain [88]. RAGE activates a cascade of intracellular reactions leading to increased oxidative stress and the production of proinflammatory cytokines via the induction of NF-κB [89].

AGEs contribute to memory impairment partially through RAGE-mediated actions. Amyloid-β crosslinked to AGEs are more toxic to neurons and form more phosphorylated tau than non-glycated AGEs [90]. Dementia and cognitive impairment may worsen when Amyloid-β binds to RAGE. When Amyloid-β binds to RAGE, RAGE produces ROS that can increase Amyloid-β, senile plaques, and NFTs [91].

RAGE may be a more sensitive biomarker of AD than Amyloid-β because it is present in early AD. Interactions between RAGE and Amyloid-β and Tau may be important in the pathogenesis of dementia and cognitive impairment [92].

The activation of RAGE leads to an inflammatory cascade that begins with the activation of phosphatidylinositol-3 kinase, mitogen-activated protein kinase, and transcription factor NF-κB, a master regulator of proinflammatory genes [93].

Both AGEs and amyloid-β are ligands for RAGE. RAGE can trigger toll-like receptors to increase inflammation. RAGE is highly expressed in neurons. When triggered by AGEs, RAGE induces the activation of the inflammatory-associated transcription factor NF-kB [94]. This can increase inflammation through TNF-α, interleukin-6, and C-reactive protein. AGEs, by binding to RAGE, are known to increase neurodegeneration as well as atherosclerosis and stroke [95].

RAGE transports circulating amyloid-β across the blood–brain barrier, where the RAGE-Amyloid-β interaction leads to oxidative stress, inflammation, and reduced cerebral blood flow [96]. RAGE is increased in the brains of AD patients. RAGE was found to act as a cell surface receptor for amyloid-β, promoting the influx of amyloid-β across the BBB from blood to brain, thereby increasing the amyloid-β burden in the brain [97]. MG, which is bioavailable from diet, could lead to a loss of selective permeability of the blood-brain barrier [98].

Dietary sources of AGEs

The highest sources of dietary AGEs were observed in beef and cheeses, followed by poultry, pork, fish, and eggs. Fatty spreads, like

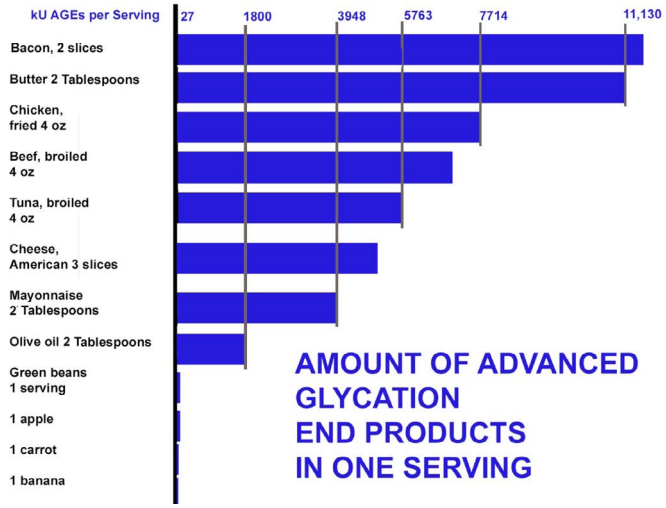

Figure 2: AGEs in one serving of selected foods

butter, are also high in AGEs. Higher levels of water and antioxidants in whole plant foods are responsible for their having the lowest levels of AGEs. The average dietary AGE intake in a cohort of healthy adults from the New York City area was recently found to be 14,700 AGE kU/day. People who consume a diet rich in fats and grilled or roasted meats could increase dietary AGE intake to more than 20,000 kU/day [99].

Advanced glycation end products accumulate in the body when meat, chicken, fish, and cheese are eaten. Meat alone can contribute 80% of dietary AGEs. Bacon contains extremely high levels of AGEs (11,905 kU/serving) [100]. In general, animal-derived foods cooked at a high temperature for a prolonged period of time and under dry conditions will have the highest AGE content [101]. By the 18th day of following the Atkins diet, the level of MG was observed to increase sevenfold, leading to an increase in AGEs [102].

Two-hundred fifty foods were tested for their content of a common AGE, N-carboxymethyllysine (CML). Grains, fruits, and vegetables were generally low in AGEs (under 28 kU/serving). In 40 type 2 diabetic patients, daily AGE intake was 18,000 kU AGE, with major proportions of AGE contributed by broiled, fried, grilled, and roasted meat. Alternative cooking methods, such as boiling and stewing, allow daily AGE ingestion to be reduced by up to 50%, while eating the same foods. A serving of chicken breast boiled for 1 hour yielded 1,000 kU AGE, while the same item broiled for 15 minutes yielded 5,250 kU AGE (Figure 2) [103].

Tissue AGE accumulation was raised by a higher intake of meat and meat products in a group of 251 healthy adults. Foods that contribute large quantities of AGEs to these diets include cheese, meats, fish, and chicken cooked by dry heat [104]. An analysis of 147 elderly individuals showed a positive correlation between serum AGEs and butter consumption [105]. Factors that contribute to the formation of AGEs in foods include high lipid and protein content, low water content during cooking, and exposure to high temperatures for short periods. Heating of proteins using methods such as frying, roasting, grilling, or baking food at high temperatures stimulates AGE formation by Schiff-base adducts and the Maillard reaction. Excessive AGE accumulation from these foods, cooked by these methods, may play a role in the pathogenesis of cognitive disorders [106].

Reduction of AGEs from foods can be achieved in 3 ways: choosing foods with a low AGE content, healthier cooking methods to minimize the production of AGEs, and a high antioxidant intake to reduce AGE formation. It has been shown that a 50% reduction in AGEs from foods decreases plasma AGEs by 30% within a month [107]. Water and moisture inhibit the reactions that form AGEs. Food preparation methods that create the fewest AGEs include: steaming, boiling, poaching, stewing, low oil stir-frying, or using a slow cooker. Foods containing water, like beans, fruits, and vegetables, have low AGE concentrations, whereas dry biscuits can contain larger amounts of AGEs. Fatty foods, such as cheese, creams, butter, margarine, mayonnaise, and olive oil, contain higher amounts of AGEs. In the category of animal products, most AGEs are seen in aged cheese, beef, eggs, and fish. The least amount of AGEs were found in fresh fruits and unprocessed vegetables.

About 10 percent of dietary AGEs are absorbed. It has been confirmed that two-thirds of absorbed AGEs are stored in tissues. Once irreversibly cross-linked, AGEs are persistent [108]. A low-AGE diet decreased serum AGEs by 30 percent, while a high-AGE diet increased serum AGEs by 65 percent in humans. These diets were similar, other than their AGE content. Alterations in circulating AGEs occurred within 2 weeks of the diet change.

Conclusion

In this paper we discuss AGE-related mechanisms that may increase AD prevalence and progression, and suggest that dietary AGE reduction may offer a new approach to combat the epidemic of AD. Reducing intake of dietary AGEs is associated with better cognitive scores in many studies. Limiting dietary AGE intake may lead to a decrease of the many brain modifications described in AD, such as amyloid-β formation and aggregation, NFT formation, increased oxidation, reduced brain perfusion from atherosclerosis, and increased inflammation. However, higher levels of AGEs can increase the neuronal toxicity of amyloid-β and protease resistance in senile plaque.

In AD, as in many other diseases, inflammation is a contributor. Both AGEs and amyloid-β can activate RAGE. When RAGE is triggered by AGEs, this can increase the expression of NF-κB, creating a cascade of inflammatory cytokines and increasing levels of C-reactive protein. The resulting increased oxidation can contribute to neuronal cell death, lowering brain volume, and can increase neurodegeneration. Conversely, there was a reduction of inflammatory markers in diets with reduced AGE content demonstrated in five studies. Dietary AGE load can be easily and safely reduced by eating less animal-derived food, as well as by choosing food processing methods that limit high or prolonged dry heat application.

Future well-designed studies are needed to confirm if dietary AGE reduction can contribute to reducing AD incidence and progression.

Conflict of interest and funding

The authors declare that there is no conflict of interest and no funding was used.

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