Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Dietary advanced glycation end products (AGE)

Evidence Summary

Modest reduction in AGE intake is a reasonable low-risk approach but significant controversy remains on whether dietary intake is a major contributing factor, particularly in those who eat a healthy diet

Neuroprotective Benefit: Very little reliable data is available for benefits of reducing dietary AGE intake; molecular pathways are not convincing for a unique role of dietary AGE.

Aging and related health concerns: Despite a reasonable rationale, limited data for substantial effects of avoiding AGE that would warrant special attention beyond other characteristics of a healthy diet.

Safety: Reducing AGE intake is almost certainly safe.

What is it? Advanced glycation end products (AGEs), also called glycotoxins, are created by the Maillard or browning reaction, when a reducing sugar reacts with a free amino group of proteins, lipids, or nucleic acids. More than 20 AGEs have been identified, falling into the categories fluorescent cross-linking, non-fluorescent cross-linking, and non-cross-linking. A commonly studied AGE is carboxymethyllysine (CML) which, compared to others like methylglyoxal (MG), is relatively stable and inert (Van Puyvelde 2014, Semba 2010).

AGEs can activate receptors like RAGE (receptor for AGE) but questions have been raised regarding the popular idea that AGE binding to RAGE elicits a positive feedback cycle of inflammation via NF-κB and NADPH oxidase. Other AGE receptors like AGER1, while less well-known can suppress oxidative and inflammatory pathways. AGE can also act independently of receptors, for example forming covalent cross-links with proteins (Poulson 2013, Van Puyvelde 2014).

The level of AGEs depends on production within the body, exogenous intake through diet, and clearance from the body through renal and enzymatic pathways. A commonly cited estimate is that 10% of consumed AGEs are absorbed and 2/3 of those absorbed AGEs are deposited into tissues, with variation depending on the specific AGE. Low-molecular weight AGEs are more likely to be absorbed However, that estimate appears to be based on ELISA methods that, while common, tend to be less accurate than other assays that rely on mass spectrometry (Poulson 2013, Puyvelde 2014, Luevano-Contreras 2010). Several pathways can help to clear AGE from the body, including the glutathione-dependent glyoxalase system (Glo I & II) and fructosamine kinases.

Neuroprotective Benefit: Very little reliable data is available for dietary AGE intake; molecular pathways are not convincing for a unique role of dietary AGE

Types of evidence:

- *0 clinical trials*
- *2 low-quality observational studies on dietary AGE intake & incident dementia or cognitive decline*
- *7+ observational studies on serum/urine AGE levels & cognitive decline or dementia*
- *2+ preclinical mouse studies*
- *Numerous studies on risk factors like diabetes*

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function?

Dementia incidence and cognitive decline have been linked to dietary intake in 2 studies but confidence in the results is limited. Dietary intake of AGE has been linked to increased decline in memory skills in 49 healthy elderly (average age 71 years) (r 0.62, p<0.001). No relationship was seen on attention, language, executive function, or overall Mini-Mental State Exam (MMSE) scores (West 2014). The risk of Alzheimer's disease was correlated with dietary AGE intake through a longitudinal cohort and through comparisons of average national diets (Perrone 2015).

AGE levels in serum, CSF, or urine have been linked to dementia status or future cognitive impairment in numerous studies (Yaffe 2011, Southern 2007, Shuvaev 2001, Bar 2003, Beeri 2011, Adams 2016, Spauwen 2015). However, these associations may not be due to increased dietary intake. AGE levels are also affected by enzymatic/renal clearance and endogenous production, both of which may be influenced by aging, frailty, and metabolic or renal morbidity. It is also too early to know whether the associations are reliable because each study varied based on patient population, type of AGE (e.g. CML vs MG vs pentosidine), source of AGE (serum, urine, CSF, or brain section), and the method used to measure AGE (e.g. immunoassay vs LC/MS). Most of studies are small pilots with poor statistics. For example, one study reported that AGE levels correlated with cognitive decline over 9 months in healthy elderly but this apparent association was heavily influenced by a few outliers whose cognitive function improved over the 9 months (Cai 2014).

Human research to suggest benefits to patients with dementia: None

Mechanisms of action for neuroprotection identified from laboratory and clinical research

In preclinical research, a diet high in AGE has been reported to accelerate cognitive decline and pathology in a mouse model of Alzheimer's disease (Lubitz 2016) and to increase glial activation and pathology in aged mice (Cai 2014). The latter study concluded that SIRT1 suppression may be an intermediary factor.

The receptor for advanced glycation end products (RAGE) has been linked to a variety of downstream pathology related to abnormal blood brain barrier function, decreased cerebral blood flow, increased neuroinflammation via several pathways, and increased beta-amyloid pathology (Deane 2012). However, RAGE binds to many ligands, including beta-amyloid, so its effects may have little to do with AGE itself. A diet high in AGEs does not always increase RAGE levels and some evidence indicates that, in physiological conditions, AGE is not usually a major activator of RAGE. Another AGE receptor – AGER1 – may help to suppress inflammation and accelerate AGE clearance but prolonged exposure to high levels of AGE may compromise AGER1 levels and activity (Poulson 2013).

APOE4 interactions: Uncertain. At least two studies reported that APOE4 status did not influence the association between endogenous AGE levels and cognition (Beeri 2011, Yaffe 2011).

Aging and related health concerns: Despite a reasonable rationale, limited data for substantial effects that would warrant special attention beyond other characteristics of a healthy diet.

Types of evidence:

- *1 meta-analysis of RCTs across healthy adults, diabetics, and CKD patients*
- *3 systematic reviews of observational and RCT data*
- *1 mouse study on lifespan*
- *reviews on preclinical studies*

AGEs have been linked many times to increased mortality and morbidity with aging. These include renal failure, blindness, cardiovascular diseases, complications of type 2 diabetes, rheumatoid arthritis, and bone fragility (Van Puyvelde 2014). Despite all these tentative links, however, controversy remains on whether dietary AGE intake is a major contributor.

In clinical trials, a change in AGE intake for 16 weeks has been reported to increase circulating TNFα levels but it generally has had no effect on other markers of inflammation like CRP or IL-6. It has also had little to no effect on biomarkers of diabetes or chronic kidney disease (Clarke 2016, Van Puyvelde 2014). Modest benefits have been seen with diabetic patients. The quality and duration of most of these RCTs is low. Observational studies may be better able to evaluate the effects of long-term dietary exposure but only 3 of 7 observational studies have found a correlation with markers of chronic inflammation, reducing confidence that dietary AGEs plays a critical role (Van Puyvelde 2014). Even when TNF alpha was increased in clinical trials, the effect did not always correlate with changes in serum AGE levels, further raising doubts as to how the dietary AGE exerts its influence and how AGE levels are monitored (Clarke 2016).

The levels of AGEs have been linked to numerous diseases as well as frailty and physical disability. For example, high levels of CML have been correlated with a 10% higher risk of at least major impairment in daily life over 14 years. However, discrepancies remain (Drenth 2016). The correlations may also have less to do with dietary intake and more to do with endogenous production or impaired clearance of AGEs.

In mice, dietary AGE can lead to oxidative stress and age-related morbidities. A calorie-restricted diet enriched with AGEs (the methyl glyoxal BSA) led to a shorter lifespan, insulin resistance, glutathione (GSH/GSSG) changes, fibrosis, oxidative stress, and other harmful effects (Cai 2008).

Safety: Reducing AGE intake is almost certainly safe.

In principle, there should be no health consequences of reducing dietary intake of AGEs in the context of a healthy diet. However, long-term effects have not been rigorously evaluated. Some studies have suggested that AGEs can function as prebiotics, helping to encourage healthy microflora in the gastrointestinal tract (Luevano-Contreras 2010).

Sources and dosing:

Common estimates on the levels of AGE may not be reliable, either because AGE levels are estimated through the serum (failing to reflect AGE accumulation in tissues and organs) or because only 1 or 2 types of AGEs are measured (failing to reflect the 20+ types of AGEs) (Poulson 2013, Engelen 2013). Much of the information has been gathered using ELISA and other immunochemical methods that have not been validated. For example, amongst people eating a traditional Western diet, vegetarians reportedly have a higher plasma concentration of AGEs than omnivores. This would be extremely surprising based on commonly cited reports for AGE levels in foods based on ELISA levels but it matches the results expected from LC-MS analysis.

The average total dietary intake of AGE in adults has been estimated at 16,000 AGE kU per day, whereas a diet rich in processed sugary foods and heat-processed meats could yield an exposure over 20,000 kU per day. Many strategies to reduce AGE intake are found in "heart-healthy" diets, for example substituting processed full-fat cheeses and meats with fish, grains, low-fat dairy, and produce. Cooking methods may further reduce AGE content of foods, for example reducing cooking times and temperatures, cooking in more humid conditions, or adding acidic ingredients like lemon juice or vinegar. Some of those cooking methods may also help to preserve nutrients that, while unrelated to AGE, are degraded during cooking (Poulson 2013).

The CML content of common foods is available here (Advanced Glycation End Products in Foods and a Practical Guide to Their Reduction in the Diet). However, the levels were calculated as CML identified with an ELISA. Similarly, a commonly cited estimate is that 10% of consumed AGEs are absorbed, with 2/3 of the absorbed AGEs deposited into tissues. That estimate also appears to be based on ELISA methods. The levels of absorption are likely higher for low molecular weight AGEs.

Bioaccumulation of AGE can be measured non-invasively using skin autofluorescence, although some challenges and possible artifacts remain with that technique (Semedo 2017).

Drugs are in development to suppress AGE formation, inhibit activity, or advance clearance. Some of these drugs, like aminoguanidine and alagebrium for AGE inhibition or breakage, have led to safety concerns. (Engelen 2013) For Alzheimer's disease, 2 separate RAGE inhibitors have been tested in clinical trials. High doses of these inhibitors worsened cognitive function. A low-dose possibly slowed decline for one drug but had no benefit with another (Galasko 2014, Burstein 2014).

Research underway: Harm from dietary AGE intake has not been conclusively proven. Major research needs include:

Standardized methods to measure AGE in foods and in people. Use of systems biology to encompass diverse AGEs rather than relying on 1 or 2 representative AGEs.

1) Evaluate cognitive decline and AGE intake in more observational cohorts and clinical trials.

2) Modest and isolated effects on inflammation have been verified in clinical trials (Clarke 2016) but whether those effects will translate into long-term health is uncertain. Systems biology approaches to track inflammation might help to interpret the results.

3) Test the effects of specific AGEs rather than broad dietary changes. Dietary AGE intake has been associated with health benefits but a low AGE diet (low in processed meats and cheeses, high in produce, fish, and grains) could yield benefits for reasons that have nothing to do with AGEs.

4) Develop drugs to mitigate the effects of AGEs or enhance their clearance, whether they are produced endogenously or consumed.

Search terms:

Pubmed: glycotoxin or advanced glycation end with cognitive, Alzheimer, dementia, aging, mortality, skin autofluorescence

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If you have suggestions for drugs, drugs-in-development, supplements, nutraceuticals, or food/drink with neuroprotective properties that warrant in-depth reviews by ADDF's Aging and Alzheimer's Prevention Program, please contact INFO@alzdiscovery.org. To view our official ratings, visit Cognitive Vitality's Rating page.