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*Review article*

# Glycative stress and anti-aging: 15. Regulation of Glycative stress. 3. Reduction of AGEs intake from food.

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## Abstract

Lifestyle and dietary habits aimed at the reduction of glycative stress are called anti-glycation. Specific measures for anti-glycation include reduction of postprandial glucose elevation, inhibition of glycative reaction, decomposition and excretion of advanced glycation end products (AGEs) produced and reducing the intake of AGEs in the diet. Since food contains nutrients such as proteins, lipids and carbohydrates, glycation proceeds during cooking, processing and storage. Melanoidins are dark brown substances in food having physiological functions such as imparting brown color to food and having an anti-oxidant effect (so-called "good AGEs"). On the other hand, heterocyclic amine, and acrylamide in food are substances that are involved in mutagenicity and carcinogenicity (so-called "bad AGEs"). Most AGEs ingested from food, are excreted in the urine. However, it is reported that AGEs contained in ingested food may accumulate in the body of patients with chronic renal failure caused by impaired renal function. In healthy persons, about 7% of the AGEs contained in ingested food may remain in the body. To suppress the effects of AGEs in food on the body, we can consider selecting a cooking method that produces fewer AGEs and the reduction of AGEs absorption in the body. Although various analytical methods have been reported for measuring AGEs in food, there are few examples where pretreatment methods of samples have been studied in detail. It is necessary to verify the effects of ingested AGEs in food, the accuracy of AGEs measurement, health condition, and eating habits of the person ingesting the food.

***KEY WORDS:*** advanced glycation end products (AGEs), food, melanoidin, absorption, excretion.

## *Conflict of Interest Statement*

The authors claim no conflict of interest in this study.

## *1. Introduction: Reduction of Glycative Stress*

Lifestyle and dietary habits aimed at the reduction of glycative stress are called anti-glycation[1], and include the reduction of postprandial glucose, inhibition of glycation, decomposition and excretion of advanced glycation end products (AGEs) produced, and reducing the intake of AGEs in the diet. This paper describes AGEs contained in food, their absorption and excretion mechanisms and the possibility of reducing the consumption of AGEs.

## *2. AGEs in Food*

Food contains nutrients such as proteins, lipids, and carbohydrates. Also, substances contained in food include reducing sugars, carbonyl compounds, amino acids, and proteins which are contained in large quantities. For this reason, the glycation in food proceeds during cooking, processing, and storage. The glycation of food is generally known as the browning reaction. Various model reaction systems and reaction mechanisms using food have been investigated, and brown substances have been separated and

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identified for the browning reaction of foods[2].

The glycation of food starts when reducing sugars generated by the decomposition of monosaccharides such as glucose and fructose are used as raw materials and seasonings, and disaccharides such as sucrose, oligosaccharides, and carbohydrates react non-enzymatically with amino acids and proteins to generate N-glucoside (***Fig. 1***)[3].

Next, N-fructoside is produced by Amadori rearrangement, and further carbonyl compounds such as ozone and furfural are formed by dehydration and deamination reactions. The carbonyl compounds that are produced react again with amino compounds as an intermediate of the glycative reaction, producing melanoidins, which are brown substances, by condensation and polymerization. Melanoidins are not pure substance, and their accurate quantification is difficult since their structure and degree of polymerization differ depending on the amino compounds from which the melanoidins are generated and the reaction conditions[4]. In addition to imparting brown color to food[5], melanoidins are substances with various physiological functions, such as anti-oxidant effect[6], cholesterol inhibition effect[7] and α-glucosidase inhibition effect[8].

In addition to melanoidins, cooked and processed foods contain various substances such as $N^{\varepsilon}$-carboxymethyl-lysine (CML), pyrraline, pentosidine, and glycative reaction intermediates[9-11]. Many of these are produced during the process of cooking food. This means that we ingest AGEs every day through food. There are several commercial beverages, and foods that contain a variety of AGEs[12]. Some AGEs in the diet are likely to be involved in the generation of reactive oxygen in the living body and the worsening of chronic diseases such as diabetic complications[13]. For this reason, the dietary habit of the intake of food containing a variety of AGEs every day may contribute to the onset of diseases.

In experiments using mice, the intake of a high AGEs diet was reported to be involved in a shortening of the lifetime[14]. Food cooked at high temperatures is known to produce heterocyclic amine[15], and acrylamide[16], which are analogs of AGEs involved in mutagenicity and carcinogenicity.

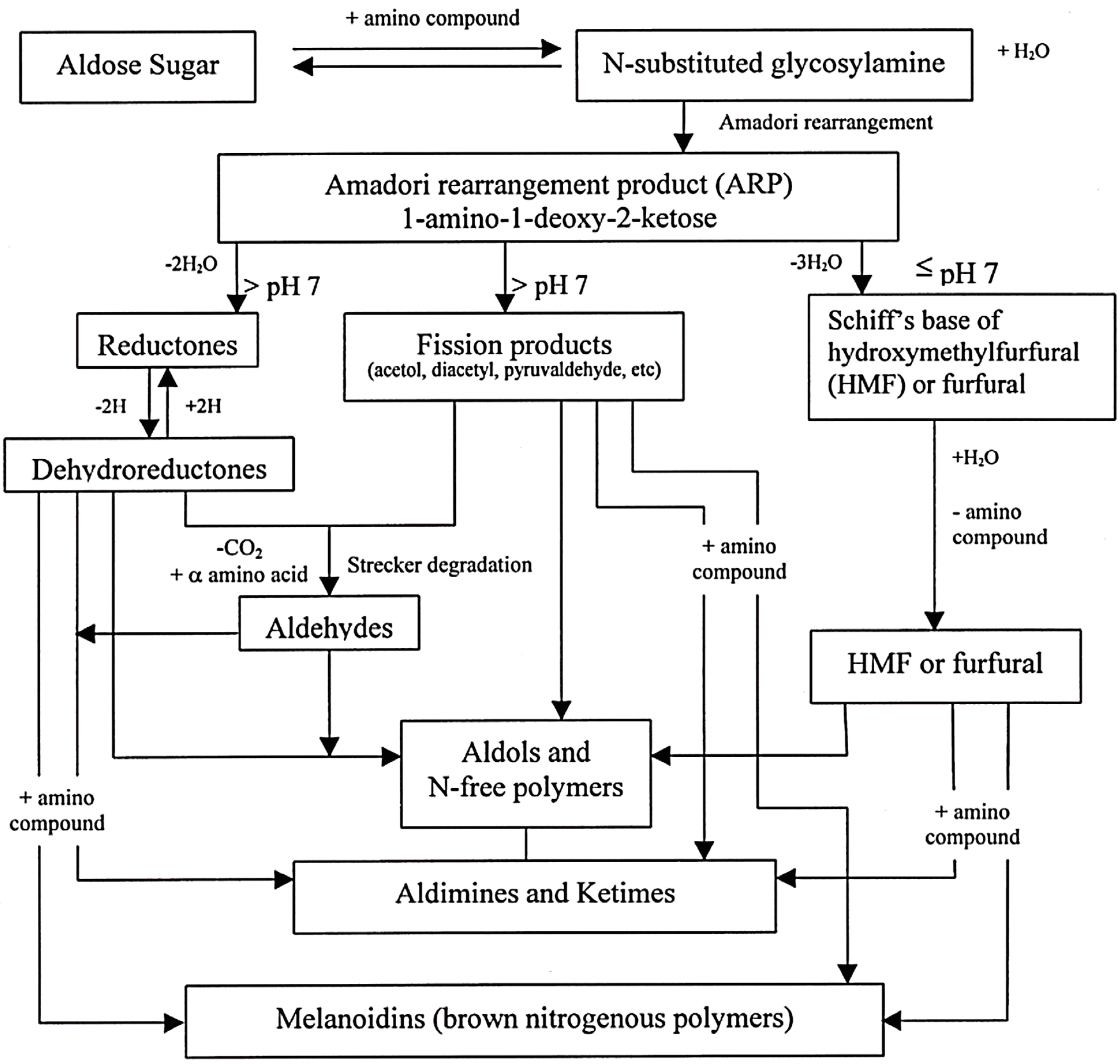


***Fig. 1.*** **General scheme of the Maillard reaction (glycation) occurring in food.**

The figure is adapted from Reference 3).

In this way, it is hypothesized that carbonyl compounds and AGEs contained in food are associated with various diseases and are called "glycotoxins" [17].

On the other hand, it has been pointed out that the coincidence between the period of human evolution when the intake of AGEs increased with the use of fire 500,000 to 800,000 years ago and the period when brain capacity increased dramatically was not by chance. In recent years, Yamamoto et al. have discovered that AGEs increase receptors for AGEs (RAGE) in the endothelium of brain capillaries and that RAGE helps oxytocin pass through the blood-brain barrier (BBB) by binding with oxytocin [18]. Oxytocin is a hormone that affects the emotions of the brain. Studies with animals have shown that a deficiency of oxytocin in the brain can reduce the survival rate of offspring due to abandonment, and it is also called the "love hormone." How diets with extremely low AGEs affect RAGE expression in the BBB is a topic of great interest.

## *3. Absorption and Excretion AGEs in Food*

There are several reports on the relationship between AGEs we ingest from food and their excretion. When seven healthy men and women restricted the intake of foods high in AGEs such as roasted food, bread, beer, and coffee for three days, pyrraline levels in the urine decreased during the period of restricted intake of food high in AGEs as compared to the unrestricted period. As a result, it was found that AGEs in the ingested food were excreted in urine [19]. We investigated the ingestion of AGEs in patients with end-stage renal disease (ESRD), and the results showed a correlation between the amount of AGEs in the food ingested and serum CML level, and also among serum CML, the amount of methylglyoxal and Blood Urea Nitrogen (BUN). In persons with impaired renal function, there is a possibility that AGEs contained in ingested food will be stored in the body [20]. Therefore, reducing AGEs in the diet for patients with renal failure is considered to be necessary for disease management.

A study was conducted in which diabetic patients and healthy persons ingested a high AGEs meal cooked by heating egg whites after adding fructose and a low AGEs meal cooked with heat using only egg whites, and AGEs in the blood and urine after ingesting each of the test foods was measured. After 48 hours following the intake of the test meal, the amount of AGEs absorbed in the blood was estimated to be 30% in diabetic patients with nephropathy, and 10% in healthy persons (*Fig. 2*) [17]. In the healthy persons, it was estimated that 1/3 of 10% of the AGEs absorbed in the blood was excreted in urine within 48 hours, and 2/3 (approximately 7%) remained in the body. The effect of AGEs contained in food can be significant when the renal function is impaired.

## *4. Inhibiting the Production and Absorption of AGEs in Food*

To suppress the effects of AGEs in food on the body, we can consider selecting a cooking method that produces fewer AGEs and inhibition of AGEs absorption in the body.

The amount of AGEs contained in various cooked foods was higher in foods rich in fat (lipids) and meat (protein) than in foods rich in carbohydrates [21]. Even when

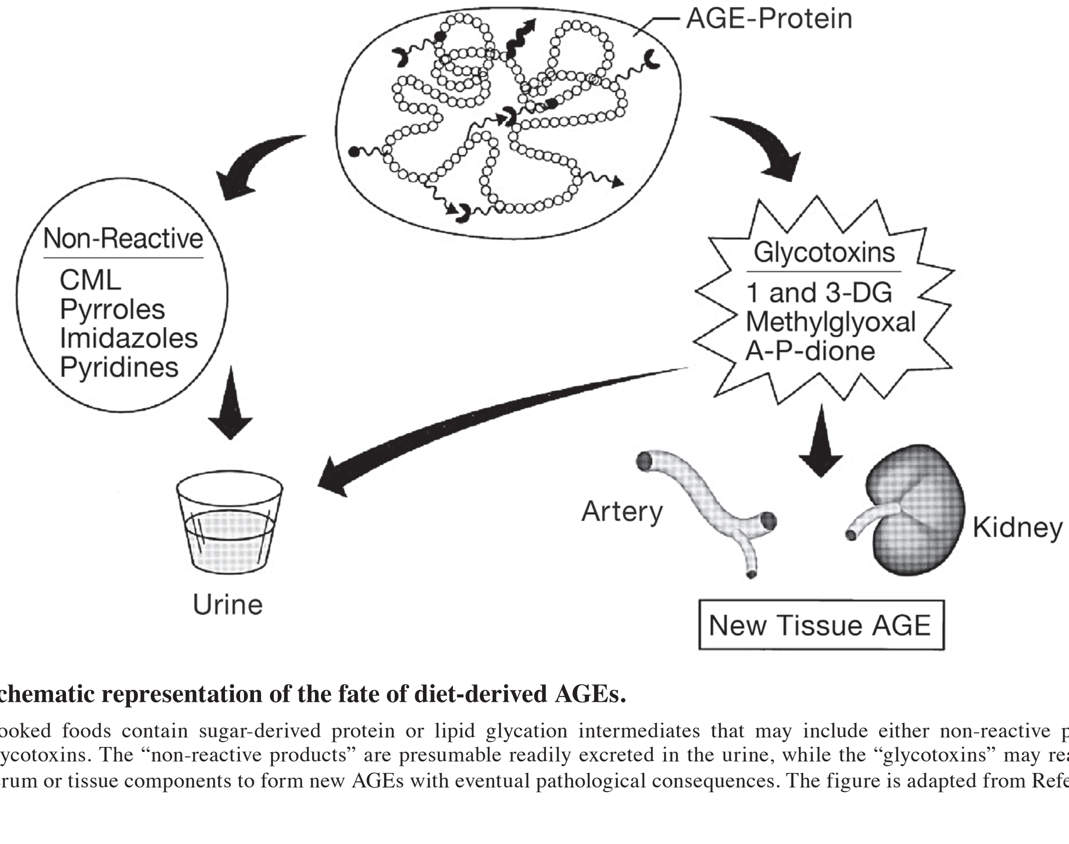


***Fig. 2.*** **Schematic representation of the fate of diet-derived AGEs.**

Cooked foods contain sugar-derived protein or lipid glycation intermediates that may include either non-reactive products or glycotoxins. The “non-reactive products” are presumable readily excreted in the urine, while the “glycotoxins” may reattach onto serum or tissue components to form new AGEs with eventual pathological consequences. The figure is adapted from Reference 17).

the same ingredients are cooked by boiling, AGEs were less likely to be produced than by frying or roasting [22]. The cooking method in which meat is soaked in lemon juice or vinegar before roasting was able to inhibit the production of AGEs that are formed by half. It has also been shown that plant polyphenols, vitamins, and phenolic acid compounds contained in food may inhibit the production of AGEs produced during cooking [23, 24].

Kremezine is known as a drug that inhibits the absorption of dietary AGEs in the body. Kremezine is a spherical carbon adsorbent obtained by oxidizing and reducing spherical fine-grained, porous carbon derived from petroleum hydrocarbons at a high temperature. It is an oral drug used to improve symptoms and delay the start of dialysis for chronic renal failure by adsorbing uremic toxins in the digestive tract and excreting it with stool. In a study conducted on patients with diabetic nephropathy who were administered Kremezine at a dose of 6 g/day for three months, a decrease in blood CML was observed [25]. Activated carbon having the same adsorption capacity as Kremezine could function as an AGEs adsorption and excretion material.

## *5. Issues with AGEs in Food*

Glycation (maillard reaction) products in food include substances with physiological functions such as melanoidins (so-called "good AGEs") and substances such as AGEs and acrolein that may damage cells and tissues (so-called "bad AGEs"). Cooking food with heat has advantages associated with food safety and taste, such as improved preservation, enhanced absorption of nutrients and adding a brown color and flavor to the food. Therefore, the effects of AGEs in food on the body need to be evaluated comprehensively. In healthy persons, about 7% of the AGEs contained in ingested food may remain in the body. However, it is necessary to take into account the effect of adsorption and excretion due to dietary fiber contained in side dishes ingested at the same time, on residual AGEs. Various analytical methods have been reported for measuring AGEs in food [26]. There are many types of proteins contained in food, which are impossible to be denatured by cooking and are impossible to extract. The coexisting lipids also interfere with various measurement methods. The Kjeldahl method is used for measuring the amount of protein in nutrition science, which quantifies the amount of nitrogen in food and converts to obtain the amount of protein [27]. However, the pretreatment method of AGEs in the diet has been examined only by a few reports. The amount of AGEs produced in food can also be reduced through the selection of ingredients and cooking methods. The effects of AGEs in food need to be considered based on the health condition and overall dietary habits of the person ingesting the food.

## *Conflict of Interest Statement*

The authors claim no conflict of interest in this study.

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