Dietary glycotoxins and infant formulas

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Abstract

Advanced glycation end products constitute a complex group of compounds derived from the nonenzymatic glycation of proteins, lipids, and nucleic acids formed endogenously, but also from exogenous supplies such as tobacco smoking (glycotoxins). Accumulating evidence underlies the beneficial effect of the dietary restriction of glycotoxins in animal studies and also in patients with diabetic complications and metabolic diseases. Composition of infant formulas and their processing methods render an extraordinary favorable milieu for the formation of glycotoxins, and the content of glycotoxins in infant formula exceeds that of breast milk by hundred folds. Data from a limited number of short-term small studies in healthy infants do not provide direct evidence of acute negative health effects of glycotoxins in early infancy. However, the effects in sensitive groups on the state of future health in adulthood remain unclear. (Turk Pediatri Ars 2016; 51: 179-85)

Keywords: Advanced glycation end products, glycotoxin, infant formulas

Introduction

Brown substances formed when food is cooked glamorize the color, odor, and taste of food, and render it more attractive. This fact was defined in 1912 by Louis Camille Maillard and is also called the Maillard reaction. During the Maillard reaction, harmful substances called Maillard reaction products emerge. These substances are currently called advanced glycation end products (AGEs) (1, 2).

The non-enzymatic and spontaneous reaction of amino groups of proteins, nucleic acids, and lipids with the other reducing sugars is called glycation. The primary products in the form of ketoamines, which are formed by way of glycation, are not stable and are transformed into AGEs by disintegrating via oxidative and non-oxidative mechanisms. Glycation products formed during smoking and cooking food at high temperatures are received exogeneously and are called glycotoxins. Figure 1 shows the main AGEs and their chemical structures (3, 4).

Glycotoxins received by way of diet are mainly formed during cooking. Fast dry-heat cooking (e.g., frying, grill-

ing, oven) leads to the formation of a much higher level of glycotoxins compared with boiling. Generally, the amount of glycotoxins increase as the flavor of food increases. Almost all kinds of food including bread, chocolate, coffee, beer, infant formulas, cow's milk, and human breastmilk contain glycotoxins to a greater or lesser extent. Table 1-7 shows the amounts of glycotoxin contained in some food stuffs that are consumed most commonly (5, 6).

Absorption and excretion of nutritional glycotoxins

Approximately 10% of the glycotoxins received by food are absorbed in the intestines. One third of the glycotoxins absorbed in the intestines are excreted by the kidneys in 48 hours. The remaining 2/3 are kept in the tissues and accumulate. The kidneys are the most important organs in excretion of glycotoxins. A portion of the glycotoxins filtered in the glomeruli are disintegrated in the tubuli and the remainder is excreted in urine. Renal diseases lead to a reduction in the excretion of glycotoxins in the urine and an increase in glycotoxins in plasma and tissues. It has been reported that the accumulated glycotoxins may have harmful effects on renal function and especially on the proximal tubuli, which are involved in glycotoxin catabolism (7, 8).

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Figure 1. Main glycotoxins and their chemical structures

CEL: carboxyethyl lysine; CML: carboxymethyl lysine; FFI: 2-(2-furoyl)-4(5)-furanyl-1H-imidazole; GOLD: glyoxal-lysine dimer; MOLD: methylglyoxal-lysine dimer

Table 1. The amount of glycotoxin in dairy products

Foodstuff	The amount of AGE (kU/100 g)
Breastmilk (fresh)	6.67
Breastmilk (frozen)	10
Cow's milk (4% fatty)	5
Skimmed milk	1
Coffee with milk	6.80
Yogurt	3
Vanilla ice-cream	34
Infant formula	486.67

AGE: advanced glycation end products

Table 2. The amount of glycotoxin in meats

Foodstuff	The amount of AGE (kU/100 g)
Uncooked veal	707
Veal cooked in water	2.222
Broiled veal	7.416
Fried veal	10.058
Big Mac	7.801
Uncooked lamb (leg)	826
Lamb cooked in water (30 min)	1.218
Broiled lamb (30 min)	2.431

AGE: advanced glycation end products

Table 3. The amount of glycotoxin in chicken and salmon

Foodstuff	The amount of AGE (kU/100 g)
Uncooked chicken	877
Chicken cooked in water (1 hour)	1.123
Fried chicken (8 minutes)	7.390
Chicken 'crispy'	7.722
Uncooked salmon	517
Fried salmon	3.083
Broiled salmon	3.347

AGE: advanced glycation end products

Table 4. The amount of glycotoxin in some foods

Foodstuff	The amount of AGE (kU/100 g)
Whole wheat bread	53
Croissant (with butter)	1.113
Pasta (12 minutes)	242
Rice (cooked for 35 minutes)	9
Parmesan cheese	16.900
Boiled egg (10 minutes)	63
Fried egg	2.749
Omelet (in olive oil)	337

AGE: advanced glycation end products

Table 5. The amount of glycotoxin in some fruit/vegetables

Foodstuff	The amount of AGE (kU/100 g)
Broccoli	226
Tomato	23
Cucumber	31
Potato (boiled for 25 min)	17
French fries (at home)	694
French fries (fast food restaurant)	1.522
Onion	36
Apple	13
Banana	9

AGE: advanced glycation end products

Table 6. The amount of glycotoxin in some beverages

Foodstuff	The amount of AGE (kU/100 g)
Apple juice	2
Orange juice	6
Cola	2.80
Filtered coffee	1.60
Tea	2
Visky	0.40
Wine	11.20
Vodka	0
Beer	1.20

AGE: advanced glycation end products

Table 7. The amount of glycotoxin in liquid oils

Foodstuff	The amount of AGE (kU/100 g)
Corn oil	2.400
Sesam oil	21.680
Olive oil	11.900
Canola oil	9.020
Sunflower seed oil	3.940

AGE: advanced glycation end products

The liver is another organ involved in glycotoxin metabolism and elimination. It performs this action through receptors found in the hepatic sinusoids and Kupffer cells. It has been shown in mouse experiments that albumin-bound glycotoxins given intravenously accumulate rapidly in the liver and this accumulation occurs in endothelial cells with a rate of 60%, in the Kupffer cells at 25%, and in the parenchymal cells at 10-15%. In addition, the liver also contributes to the production of inflammatory

molecules, which are formed as a result of oxidative stress caused by glycotoxins (9, 10).

The effects of glycotoxins on health

Glycation is the most important reason of spontaneous damage in proteins. Proteins can be repaired by elimination of protein-bound fructosamine and other ketoamines by fructosamine-3-kinase and similar enzymes. Protein glycation is an inevitable mechanism despite enzymatic repair mechanisms and glycotoxins continue to increase in conditions including diabetes as a result of increased glucose concentration. Proteins that have been exposed to glycation lead to an inflammatory response by way of AGE receptors (RAGE) and cause gene activation. As a result, various inflammatory diseases develop. It is currently thought that glycotoxins are involved in the pathogenesis of a great number of diseases including diabetes complications, renal failure, hepatic diseases, neurodegenerative diseases, eye diseases, and cancer (5, 11).

Diabetes

It has been shown that a correlation exists between AGEs and vascular, renal, retinal, and neurologic complications of diabetes. The role of AGEs in the progression of diabetic complications (diabetic nephropathy, peripheral neuropathy, cardiomyopathy, peripheral artery disease, eye complications, and atherosclerotic disease) is well known. It has been shown that glycotoxins in the diet lead to the development of insulin resistance and type 2 diabetes in experimental animals. It was shown that inflammatory markers were reduced, insulin resistance was improved, and plasma insulin levels were decreased in patients with diabetes when ingested dietary glycotoxins were reduced (12-14).

Renal diseases

A portion of AGEs are eliminated from organisms via the kidneys. Advanced glycation end products accumulation in the kidneys may lead to damage through the AGE-RAGE relationship and in situ glycation. In addition, advanced glycation end products may cause direct damage in the matrix proteins in renal tissue via cross-links. The relationship between chronic renal disease and AGE is a viscous cycle; as AGEs increase, glomerular filtration decreases and this fires the increase in AGEs. In contrast, renal damage and mortality related with glycotoxins were observed to be decreased in relation with a decrease in oxidative stress and inflammation when intake of glycotoxins were decreased (15-17).

Hepatic diseases

A relationship between AGEs and hepatic diseases has also been shown in experimental studies; changes ranging from simple adiposity to biochemical disturbances

and even cirrhosis may occur. Presence of AGEs has been shown in the liver of patients with non-alcoholic steatohepatitis using immunohistochemical methods, and serum AGE levels were found related with the severity of hepatic disorder (18-20).

Polycystic ovarian syndrome

Increased AGE levels found in women with polycystic ovarian syndrome are positively related with insulin resistance. Increased AGEs have been demonstrated in polycystic ovaries in women with polycystic ovarian syndrome using immunohistochemical methods (21, 22).

Neurologic diseases

Advanced glycation end products have been found related with the pathogenesis of many neurologic diseases (Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, peripheral diabetic retinopathy). A possible neurotoxic effect resulting from amyloid glycation and oxidative stress is blamed in the pathogenesis. It is thought that neurodegenerative diseases can be prevented in individuals aged over 60 years by reducing glycotoxins ingested with food (23, 24).

Eye diseases

Advanced glycation end products have been found related with loss of vision, macula degeneration, formation of cataract, diabetic retinopathy, and glaucoma. The pathogenic mechanism has been proposed to be associated with the accumulation of AGEs in tissues in the eye, cross links formed with extracellular matrix proteins, and oxidative stress. In a study conducted with mice of different ages, high amounts of AGEs added to the diet were shown to lead to an increase in AGEs and RAGE in peripheral tissues and different tissues in the eye (25, 26).

Cancer

The effect of glycotoxins on the risk, development, and progression of cancer is not known clearly. In vitro studies conducted with some cancer cells suggested that AGEs might have a potential effect on cancer proliferation, migration, and invasion. However, studies conducted with humans were inconclusive, which would be sufficient to explain this issue. Nevertheless, it has been shown that AGEs can accumulate in some tumor tissues and this accumulation is greater in malignant tumors such as prostate cancer, and less in benign tumors. It is assumed that glycotoxins enhance development of cancer by stimulating the inflammatory cycle by way of oxidative stress. In some studies, it has been proposed that an inverse relationship is present between soluble AGEs and the risk of pancreatic and colon cancer. However, this relationship has not been proven with other studies (27-29).

Measurement of glycotoxins

The amounts of AGEs in the blood, urine, and tissues can be measured with very different methods. These include:

1. Methods based on fluorescence measurement,
2. Methods that use AGE-specific mono or polyclonal antibodies in enzyme-linked immunofluorescence assays (ELISA),
3. High-pressure liquid chromatography. The most sensitive measurements are those based on mass spectroscopy.

The best method for measuring AGEs in tissues is biochemical examination of biopsies (30-33).

How can the production of glycotoxins be decreased?

Diet

The amount of AGEs can be reduced by changing cooking techniques (cooking at low temperatures, cooking slowly, boiling or cooking with steam) and eating food with low AGE content (consuming vegetable, fruit, fish, legumes, bread, and low-fat milk/dairy products, and reducing or avoiding sugary products, bakery products, processed food, cakes, pies, muffins, instant sugary drinks, packed meat products, cheese, fats and frozen food) (5, 34).

Drugs

Drugs that block the formation of AGEs

Aminoguanidin was the first drug shown to inhibit AGEs and it was shown to prevent diabetic complications including retinopathy and nephropathy in animal experiments. In addition, NN-(2-Acetamidooethyl) hydrozinecarboximidamide hydrochloride (ALT-946), 3-enzyloxycarbonylmethyl-4-methyl-thiazol-3-ium bromide (C36), Hydroxymethylglutaryl-coenzyme A reductase inhibitors (statins) and pyridoxamine are other substances that have been shown to reduce or prevent the harmful effects on the kidneys and cardiovascular system through AGE inhibition in experimental animals in different studies (35-39).

Drugs that break down cross-links

N-phenacylthiazolium and its derivative N-phenacylthiazolium (alagebrium (3-phenacyl-4,5-dimethyl-thiazolium chloride) or ALT-711 have been shown to have positive effects on the renal and cardiocascular complications of diabetes in animal experiments and breaks down cross-links (40, 41).

Drugs that cause receptor blockage

It is thought that some drugs have suppressive effects on RAGE expression. These include antihypertensive drugs

(calcium channel blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers), anti-diabetic drugs (thiazolidinedione) and cholesterol-lowering drugs (statins). These drugs contain soluble RAGE and may prevent various diabetic complications by preventing AGE from binding to RAGE (42-44).

Infant formulas and glycotoxins

Formula products are prepared with cow's milk and targeted to imitate breastmilk. A higher level of AGE formation occurs in formulas compared with normal milk because of the additives included (e.g., protein, amino acids, nucleotides, iron, vitamin C, carbohydrates, lipids), and exposure to high temperatures during preparation and sterilization. The amount of AGE in formulas varies by brand and by the characteristics (depending on whether the formula is liquid, powder, hydrolized, and whether it contains lactose). Generally, a higher level of glycotoxin has been found in liquid formulas, hydrolized formulas, and in formulas with a high lactose, whey protein, iron, and vitamin C content. It has been shown that normal infant formula may contain up to 100-fold higher carboxymethyl lysine (CML) compared with breastmilk. The storage conditions of formulas also affects CML content. It has been shown that the CML content of formulas may increase by 40% throughout the shelf life. Reheating of prepared formula also leads to an increase in the CML content (45, 46).

It has been shown that newborns receive approximately 15 kU AGE daily for each kg of their body weights from breastmilk and this value reaches 76 kU at the age of six months, and 111 kU at the age of 12 months (47). According to another study, the amount of CML received by an infant aged between 3 and 10 months who is fed with breastmilk does not exceed 0.004 mg/kg body weight. Between the ages of 3 and 10 months, the daily amount of CML received by an infant fed with a formula containing low CML (50-110 ng CML/mg protein) increases to 0.27-0.33 mg/kg, and it may increase to 1.3-1.5 mg/kg in infants fed with a formula containing high CML (160-630 ng CML/mg protein) (48).

In a study in which infants who were exclusively fed with breastmilk or formula were compared, insulin sensitivity was found increased and plasma CML levels were found lower compared with infants fed with formula. This finding suggests that being fed with formula increases insulin resistance. However, it was observed that serum CML level was increased two-fold at the age of 12 months in infants who were fed with breastmilk, but plasma insulin, glucose, and the HOMA index, which indicates insulin resistance, did not change. In infants fed with formula, it

was observed that the CML level was decreased, but insulin sensitivity was not different from infants who were fed with breastmilk. These findings do not confirm the argument that AGE-rich food affect insulin sensitivity in infants (48).

Healthy infants fed with formula have been shown to have increased kidney size at the age of three months compared with infants fed with breastmilk. This renal hypertrophy disappears up to the age of 18 months when infants are fed both with breastmilk and formula. In recent studies, renal dimensions were found increased at the age of six months in infants who were fed with formula that had high-protein content, but those of infants fed with formulas with low protein content were not different compared with infants fed with breastmilk. The kidneys are one of the organs in which AGEs are both excreted and deposited. This deposition is known to be related with diabetic nephropathy in adults. It is thought that renal hypertrophy in infants fed with formula might be related at least with increased AGE load (49, 50).

Significantly higher levels of oxidative stress and inflammation were found in the kidneys of experimental animals with in utero growth retardation who were fed with formulas containing high levels of AGE compared with those fed with formulas containing low levels of AGE; the authors recommended the use of methods that would form the lowest level of AGE in preparation of formulas for infants with in utero growth retardation or for premature babies (51).

Conclusion

It has been clearly shown that advanced glycation products are extremely closely related with diabetes and its various complications in adult studies. A limited number of studies have shown that high intake of AGE during infancy by way of infant formulas can be tolerated in some way and does not at least lead to a known damage during this period. However, further studies are needed to understand long-term effects. Intake of high levels of AGE in adults is known to be related with aging of the organs and the organism as a whole. Therefore, it will be possible to partially protect babies right from the beginning of life from diabetes and similar diseases and their complications with precautions including production of formulas with methods which would form the least level of AGE (application of less heat, preparation of the components separately), paying attention to storage conditions, preferring powder formulas instead of liquid formulas, avoiding hydrolized formulas unless necessary and avoiding reheating of reconstituted formula in feeding bottle.

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