REVIEW PAPER

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Influence of food-derived advanced glycation end products on health

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Abstract

Introduction. Advanced glycation end products (AGEs) are compounds formed endogenously in the human body. Besides this source of AGEs, they also exist in food and can be generated during cooking. Enhanced endogenous generation and intake of dietary AGEs have physiological impact on human health and are associated with progression of many diseases, including diabetes and its complications.

Aim. The purpose of this review is to the present the current state of knowledge about the various negative effects of advanced glycation end products on human health.

Materials and methods. This study is based on analysis of literature reporting the content of AGEs in food and high or low AGEs dietary interventions in human and animal subjects.

Results. Literature data present databases gathering description of AGEs determinations in various types of food.

Conclusions. Excessive consumption of AGEs-rich products, especially abundant in protein and fat or cooked for a long time at high temperature, may contribute to the deterioration of human health, including development of hypertension, insulin resistance, and diabetic complications.

Keywords. advanced glycation end products, AGEs, CML, diabetes, glycation

Introduction

Advanced glycation end products (AGEs) are a heterogenous and complex group of compounds that are generated via a spontaneous reaction called glycation or "Maillard reaction". Glycation occurs when aldehyde or ketone group of sugar reacts with protein, nucleic acids and lipids. The most important sites which can be glycated including N-terminal amino groups of protein, especially lysine and arginine, guanyl bases of nucleotides, and amino groups of phospholipids. Also, two reactive dicarbonyl - glyoxal and methyloglyoxal are key-precursors of AGEs formed during glycation.[1]

The most common and well characterised AGEs include Nε-carboxymethyllysine (CML) and Nε-carboxyethyllysine (CEL). CML was described for the first time in 1985 by Ahmed. It is formed in oxidative cleavage of fructoselysine or during the reaction between glyoxal and amino group of lysine. Ahmed was also the first to describe CEL in 1997. CEL is an homologue of CML and it is formed during the reaction of methylgly-

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oxal with lysine residues of protein.[2] Glycation occurs in physiological conditions, however its severity and extent are associated with aging and several diseases states such as diabetes and its complications, Alzheimer's and Parkinson's diseases, cardiovascular diseases and chronic kidney disease.[3-7]

High levels of AGEs in serum are associated with a reduction of insulin secretion and induction of insulin resistance in human subjects.[8,9] Recent reports indicate that AGEs inhibit the expression of anti-apoptotic proteins and, in this way, regulate the survival of oral cancer cells.[10] Furthermore, AGEs promote proliferation, migration and invasion of breast cancer cells what indicate that AGEs may underlie the pathogenesis of not only diabetic complication but also cancer in diabetes.[11]

Harmful effects of AGEs are dependent of mechanisms of action. Firstly, increased generation of AGEs may be independent of receptors and leads to changes in protein structure, function and stability. Glycation of proteins increases of their molecular weight, alters resistance to proteolysis and ligand binding, decreases hydrophobicity, and induces of protein aggregation.[12] Second mechanism requires interaction between AGEs and receptors for advanced glycation end products (RAGE). This reaction after activation of kinase pathway, leads to the activation of the transcription nuclear factor kappa B which promotes transcription of proinflammatory factors and causes an increase in the formation of reactive oxygen species. Finally, enhanced oxidative stress and inflammation intensify the deleterious effects of AGEs.[13]

Food-derived AGEs

Advanced glycation end products are generated endogenously, but AGEs also can be formed exogenously and get into the human body with food. One of advanced glycation end products, CML, is one of the most abundant in human body and it was one of the first to be described in food.[14] Both CML and CEL are the most frequent and generally accepted markers for measurement of concentration of glycation products in meals and well-representatives for whole group of AGEs.

The gastrointestinal tract is considered the first barrier against harmful dietary glycation products. Yuan et al observed that, in rats fed with diet high in AGEs, the highest content of CML in the gastrointestinal tract occurs in the ileum, little less in the jejunum, while the lowest level of CML is in the stomach.[15] It is known that approximately 10% of ingested AGEs are transported into bloodstream and only 30% of absorbed AGEs are excreted with urine via kidneys.[16] Rest of ingested AGEs remain in the body. Glycation products may bind to proteins and successively accumulate in organ tissues such as kidneys, liver, bone, heart, brain, muscle, tendons and skin what results in impairment of their functions.[17]

The western style diet, due to high content of in meats and processed foods, is rich in glycation products known as glycotoxins. Literature reports extensively describe the content of various glycation products in various food and methods for their determination such as liquid chromatography which is considered a gold standard for measurement of AGEs in samples. Information about tested products is collected in robust databases that contain more than 1,600 beverages and foods.[18] Generally, the highest content of glycation products is observed in confectioneries, what is connected with heating of products rich in reducing sugars and flour at high temperature for a long time.[18] The highest content of CML, CEL and Nδ-(5-hydro-5-methyl-4-imidazolon-2-yl)-ornithine is found in black pudding, different types of cereals, peanut butter, biscuits and rusk.[19] Products high in AGEs also include higher-fat and aged cheeses, butter, cream cheese, margarine, and mayonnaise.[20] Among drink beverages, drinks containing lactic acid bacteria and highly carbonated are the richest in AGEs.[18] Beef is considered a meat with the highest AGEs level among different types of meat, while lower amount of CML is observed in poultry, pork, fish.[20,21] The lowest average content of CML is noted in fruit and vegetables as well as juices.[22] Breads, yogurt, ice cream and milk belong to group of products which are relatively low in CML.[20]

Various types of foods in Western diets are exposed to thermal processing what makes food microbiologically safer as well as improves aroma, taste and appearance. It is known however, the cooking methods have impact on the level of AGEs. Chen and Smith proved that frying and broiling of meat at higher cooking temperature cause an increase in the CML content.[21] Data show that oven cooked pork meat has higher content of AGEs than meat prepared in the autoclave and braised.[23] Among methods which generate low amount of AGEs are steaming, stewing, and boiling. Moreover, preparation of meat dishes with the addition of sauce such as soybean or tomato sauce, markedly increase the generation of glycation products.[24] However, formation of new AGEs is prevented by addition of AGEs inhibitors or acidic solutions of lemon juice and vinegar to the dish.[20] Similarly, it is known that many compounds of natural origin, especially polyphenols, may prevent or inhibit the formation of glycation products.[25]

Intake of diet high or low in AGEs

The influence of intake of a diet low or high in AGEs on human and animal health is described in many reports. Intake of dietary AGEs is related to enhanced formation of pro-inflammatory mediators, which contribute to tissue injury in patients with diabetes.[26]

The study conducted on group of 450 participants reveals that higher dietary intake of AGEs is correlat-

ed with higher levels of various types of AGEs in plasma and urine. A positive correlation between intake of CML, CEL and Nδ-(5-hydro-5-methyl-4-imidazolon-2-yl)-ornithine in meals and their free levels in blood plasma.[27] Similarly, 3 months intake of a diet low in AGEs leads to reduction of serum CML and methylglyoxal concentration in adult obese men. Combination of meals low in glycation products and exercise also causes a decrease in triacyloglycerols and an increase in the high-density lipoprotein.[28]

On the other hand, Semba et al. observed that diet abundant in AGEs causes no significant changes in serum and urinary glycation products concentration in healthy adults group. The authors have reported that after 6 weeks of diet containing about 4 times more AGEs did not lead to changes in endothelial functions measured by peripheral arterial tonometry, level of inflammatory mediators as well as endogenous secretory and secretory receptor for AGEs. However, participants who had meals low in AGEs showed a significant decrease in the serum and urinary CML concentration when compared to baseline.[29] Furthermore, the same researchers after investigating diet and physiology of 261 subjects proved that, generally, intake of food-derived AGEs such as fried foods and meat products did not increase of the CML concentration in serum and urine.[30] Surprisingly, Sebekova et al. proved that AGEs level in plasma is higher in vegetarians than omnivores.[31] It might seem that, based on cooking techniques (higher temperature and longer heating time), participants who eat meat and meat-derived products should have higher concentration of glycation products in blood plasma. Overweight children and young people have the same concentration of plasma RAGE and lower level of fructoselysine and CML in plasma due to enhanced removal of modified proteins via kidneys what is manifested by proteinuria as compared to controls.[32]

Intake of food-derived AGEs by human subjects is associated with increased risk of hypertension and arterial stiffness and inflammatory activation what lead to a vascular dysfunction in patients with type 2 diabetes.[33,34] It is known that, consumption of a food low in AGEs decreases insulin resistance in overweight women as well as improves cardiometabolic parameters.[35,36] Likewise, animals representing model of diabetes fed with meals rich in AGEs exhibits deteriorated vascular complications manifested by alternations in structure of endothelial and mesangial cells as well as podocytes in renal cortex.[37] Moreover, analysis of embryos of mice fed with diet containing 3% of advanced glycation end products shows defects in neural tube development in the absence of hyperglycemia.[38] Also, intake of diet abundant in glycation products in experimental mice causes an accumulation of AGEs in Achilles tendon resulting in alternation of its properties and the development of injuries.[39] Induction of

systemic inflammation manifested by elevated secretion of pro-inflammatory cytokines and chemokines and liver inflammation in the absence of steatosis have also been found in case of mice fed a high-AGE diet.[41,42] Nevertheless, in mice with experimental induced diabetes, diet low in AGEs prevented diabetic nephropathy and was considered responsible for low AGEs content in kidneys.[42] Similarly, perinatal exposure to low-AGEs diet decreases AGEs content in serum and immune cell infiltration into the pancreatic islets as well as improves insulin, proinsulin and glucagon secretion in mice susceptible to type 1 diabetes.[43] Evidence from animal and human studies suggest that dietary AGEs could play a role in development of various disease states. It appears that reduction of the consumption of food-derived AGEs is important to significantly reduces their harmful effects in the human body.

Conclusions

Glycation leads to formation of advanced glycation end products which exist in food in addition to being endogenously produced. Long-time cooking at high temperatures causes an increase in the AGEs content in meals. Meals abundant in reducing sugars, protein and fat have a higher content of glycation products. Diet high in AGEs, due to their reactivity and harmful potential, is associated with higher content of AGEs in plasma and urine and has deleterious effect on human health resulting in induction of hypertension, insulin resistance, and diabetic complications. On the other hand, animal and human studies indicate that the restriction of dietary intake of AGEs may improve health conditions. Consumers, especially patients with diabetes, should remember about choosing products with low content of glycation products. It is also important to use the cooking methods generating low AGEs content such as steaming, stewing, and boiling instead of broiling and frying.

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