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Maillard reaction. Pathogenic effects.

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Abstract

Maillard reaction. Pathogenic effects. Certain organoleptic modifications by way of processing and cooking foods at high temperatures in dry heat, make them especially appetizing and object of addiction. It results from Mayllard reaction, or glycation, consisting on the non-enzymatic union between carbonyl groups, mainly from reducing sugars as glucose and fructose, with the amino groups of proteins and nucleic acids. In addition of physical changes, also the chemical structure and function of these compounds are changed. Besides exogenous glycation generated during the cooking of foods, recently *in situ* glycation has been reported in the intestinal lumen during digestion, when certain non-glycated foods are combined with fructose at the time of ingestion. In addition, endogenous glycation, which correlates in the extracellular mainly with blood glucose and in the intracellular with glycolysis metabolites and fructose, is especially significant. Since the 70s, with the frequent sucrose replacement by fructose, much more reactive than glucose, the presence of glycation products in processed foods and soft drinks increased. Pathogenic effects of these compounds, also called glycotoxins, are known to contribute to oxidative stress and inflammation. This

increases progression of chronic diseases, well documented in diabetes, renal insufficiency, cardiovascular disease and ageing process and are being explored in many other chronic diseases as neurodegenerative diseases and early ageing. Based on the knowledge achieved so far, measures to preserve health are described by attending ways of cooking and processing foods, besides recomendations for the habits and antioxidants dietary intakes for inhibition or antagonism on glycotoxins.

Keywords: Mayllard reaction, glycation, glycotoxins, oxidative stress.

Introduction:

Maillard reaction[1], or glycation, consists of the non-enzymatic union between carbonyl groups, mainly aldehydes or ketones from reducing sugars as glucose and fructose, with amino group of proteins and nucleic acids. Carbonyl groups are also generated during oxidative degradation of lipids. Glycation is related to concentration and contact time of involved substances, and the reaction is strongly accelerated in conditions of high temperature and low humidity (dry heat). Different foods show accelerated generation of these by-products at temperatures above 100-120°C, and especially at 140°C. The reaction is observed in grill, oven, griddle or fry cooking, and is facilitated by alkaline pH, copperware and ironware. Cooking in copper or iron pots and adding sodium bicarbonate (as is usual in the elaboration of *dulce de leche*, a caramel made of sweetened milk), gets a darker final color through glycation.

Glycation is a well-known phenomenon in gastronomy, being responsible of toasted color with different shades of brown, due to pigments called melanoidins. Glycation, as well as lipid products derived from oxidation[2], have influence in the appetizing changes in flavour and aroma that take place during the cooking of food products so different as roasted beef, *croissants* and french fries.

Glycation generates three types of

products: unstable and reversible compounds (Schiff bases), stable and potentially reversible compounds (Amadori products), and irreversible compounds (AGEs: Advanced Glycation End-products).

Since 1976 it has been observed that a fraction of total hemoglobin is in the form of glycated hemoglobin (this denomination is preferred over "glycosylated hemoglobin" to reflect the correct non-enzymatic process). Increased levels of glycated hemoglobin (HbA1c) in diabetes correlates with elevated glucose levels, and is used by clinicians to monitor diabetes treatment[3]. Glycated compounds originated in lipid catabolism are known as ALEs (Advanced Lipooxidation End-products)[4].

Glycation products can be measured in blood, urine and tissues by various methods, such as enzyme immunoassay, mono and polyclonal antibodies, autofluorescence, chromatography, or mass spectrometry, which is the most sensitive one. Carboxymethyl lysine, glyoxal and methylglyoxal are the best studied AGEs[5].

Alcohol overconsumption, especially stout beer and sugar-rich liquors, is, through acetaldehyde production, an important contributor in AGEs generation[6]. Glycation products are retained in several organs and tissues or are partially metabolized into second-generation products that are excreted in urine[7, 8].

Glycation research has interest in clinical medicine, especially in relation to diabetes. Glycated products are metabolized and excreted, but also deposited in different tissues and organs.

Exogenous Glycation. Role of Fructose

Exogenous glycation generates dietary AGEs (dAGEs). It has always been considered that this process took place almost exclusively during food cooking. Recently, it has been observed that a non-glycated food such as ovalbumin, ingested with apple juice, produces a rise of glycated compounds in serum and urine. It is considered *in-situ* glycation within the intestinal lumen, followed by systemic absorption of adducts. AGEs are generated in *in vitro* models of gastrointestinal digestion of ovalbumin in the presence of fructose (a carbohydrate more reactive than glucose). Chlorogenic acid, a main phenolic compound of *yerba mate* (*Ilex paraguariensis*), can inhibit the reaction, almost as potently as aminoguanidine, a well-known inhibitor of glycation[9-12].

Exogenous glycation, normally generated in foods during cooking, can also be produced in the intestinal lumen, due to fructose action over protein sources.

Endogenous Glycation

Under physiological conditions, endogenous glycation is produced in small quantities during metabolic processes, both outside and inside cells. Extracellular glycation is the result of interaction between blood glucose and plasmatic proteins, and, consequently, increases with hyperglycemia. Fructose plays a minor role, since its serum concentration is less than 1% that of glucose, but has an important place in intracellular glycation. In the intracellular, glycolysis metabolites from glucose 6-phosphate and dicarboxylic precursors, glyoxal and methylglyoxal, have reactive activity for glycation[13].

The special significance of fructose is that, besides being significantly more reactive than glucose, its intracellular concentration increases not only after ingestion, but with hyperglycemia, since glucose activates aldose reductase, that generates fructose from glucose[13].

Endogenous glycation occurring out of cells is related to glucose levels, while within cells the process has relation with glycolysis metabolites and fructose levels.

Pathogenic Effects

Glycation end-products, known also as “glycotoxins”, are potentially harmful to health. They are highly reactive molecules that behave as electron donors during free radicals generation. The process contributes to oxidative stress, a main factor of cellular damage, that also enhances endogenous glycation.

AGEs activate specific receptors: RAGEs (Receptor Advanced Glycation End-products)[14], proinflammatory cytokines (interleukin 1, interleukin 6), tumor necrosis factor-α, insulin-like growth factor-1 and C reactive protein (CRP), that alter cell membranes permeability and vitality. Interaction AGEs-RAGEs mediates most biologic effects, including free radical generation, thus closing a vicious circle.

Free radicals also stimulate platelet activation and promote thrombosis. They contribute to vasoconstriction through reduced nitric oxide synthesis in smooth muscle of vessels wall, and through inhibition of plasminogen, an essential fibrinolytic compound.

Proinflammatory actions, thrombosis promotion and atherosclerosis are responsible of tissue damage, notably in liver, kidney, brain, lens and connective tissue, especially skin, cartilage and tendons[4].

AGEs, plasma and tissue proteins, in cross linked forms, interact with RAGEs located on endothelial surfaces especially of collagen, which may lead to microvascular or macrovascular disease, articular loss of flexibility and loss of mobility in joints.

Altered structural proteins in connective tissue interfere with osteoblastic differentiation and bone remodelling, and lead to skeletal fragility[15].

Mediated by a chain of reactions, alterations are produced in protein chemical structure, and amino acids lose their normal three-dimensional configuration, leading to functional derangements with potential pathogenic effects. Nucleic acids may also suffer transformation in adducts, depurination and consequent deletion or mutation[16].

It has also been observed reduced enzymatic activity in calcium pump, calmodulin and superoxide dismutase, and increased activity in aldose reductase. Changes in superoxide dismutase increase noxious effects of free radicals, alter cell membrane permeability, and modify (along with abnormalities in calmodulin and calcium pump) intracellular calcium concentration, a process that influences muscle contraction, genic expression, cell differentiation and neuronal functions[17]. Enhanced aldose reductase activity increases fructose concentration.

The greater or lesser protein involvement is related to protein half-life. Schiff bases and, to a lesser extent, Amadori products —mostly unstable and reversible products— may be observed in high turnover, short half-life proteins, implicated in cell renewal, like plasmatic proteins, red cell proteins, and proteins in organ such as intestine, skin and liver.

AGEs are observed in months or years of contact with long half-life proteins, such as those in lens, collagen or myelin sheaths, and also with nucleic acids. AGEs accrual in human tissues suffering micro and macrovascular damage —initially described in relation to diabetes— has actually been identified in advanced stages of renal disease, neurodegenerative diseases, chronic pulmonary obstraction, brain impairment, cardiovascular disease, cataracts, atherosclerosis and premature ageing, especially in skin and vascular endothelium[18-21]. Ageing can be viewed as a deleterious circle made up of oxidative stress, free radicals, mitochondrial damage and increasing intracellular calcium, boosted by glycation.

AGEs slowly affect tissue renewal, and long half-life proteins in dermis are especially prone to damage due to ultraviolet radiation-enhanced glycation.

Elderly persons with Type II diabetes and compromised cognition show AGE, RAGE and CRP high levels, correlated with HbA1c values[22]. In senile plaques and neurofibrillary

bundles and beta-amyloid plaques found in Alzheimer disease, AGE deposition is three times that of controls[23].

So far less investigated, AGE deposits seemingly play a pathogenic role in other neurodegenerative diseases, such as Parkinson disease[24], Lewy bodies dementia[25], amyotrophic lateral sclerosis[26], Huntington disease[27] and Creutzfeldt-Jakob disease[28]. Elevated serum levels of AGEs and RAGE activation have been described in polycystic ovary syndrome[29].

Diabetic patients are especially susceptible to glycotoxins, due to higher endogenous production; diabetic treatment, blood glucose control and dAGE reduction are relevant in prevention of chronic complications, like kidney disease, retinopathy and neuropathy.

Insulin-dependent diabetic patients with kidney involvement and retinopathy may present with articular stiffness in hands. This evident and simple semiological sign is important for diagnosis and can be further confirmed by palmar impression, lacking limiting marks between phalanges[30, 31].

In diabetic nephropathy, after an initial stage with functional alterations, a second stage ensues, characterized by thickening of basal membrane, mesangial expansion and changes in glomerular arteries. These lesions can not be attributed to immunological mechanisms, and alteration in structural proteins seems to be the main pathogenic factor.

Pregnant women with poor controlled gestational diabetes can give birth to newborns with congenital malformations, such as caudal regression sequence, from simple form (sacral agenesis), to most severe (sirenomelia or Mermaid syndrome). It is not known if these malformations represent a defect of caudal blastema, a defect in posterior mesoderm, an alteration of structural proteins in connective tissue or nucleic acids alterations[32].

dAGE reduction is relevant not only in diabetes, but also in renal failure. Low dAGE diets in patients on continuous peritoneal dialysis for advanced renal failure correlates with better values of urea, creatinine, total proteins, albumin and phosphorus[33].

Patients with chronic renal failure may suffer especially with reduced elimination of noxious carbonyl-group compounds, highly reactive for glycation (carbonyl stress). AGEs are pathogenic compounds responsible for induction and progression of kidney damage and cardiovascular complications. AGE-linked fluorescence can be detected in skin, and can be used as a prognosis marker of vascular damage and kidney failure in patients on hemodialysis or renal transplantation[34].

Within cells, AGE-associated damage is found especially in mitochondria, derangement of mitochondrial metabolism decreases energy production and conseqwently cytoplasmic glycolysis increases. Without access to Krebs cycle and respiratory chain,, production of lactic acid as end-product, conforms the basis for cancer metabolic theory[35,36]. AGEs induce apoptosis, normally a mechanism for replacing aged or damaged ce3-lls, for cell renewal during maturation and growth, and for defense in the face of a viral attack.

Research studies modifying diet to provide low or high dAGE, have not consistently shown correlation with serum or urine AGE levels, nor significant changes in inflammation markers, peripheral arteries tonometry or endothelial function[37]. These discordant observations have prevented definitive conclusions. Some experts have speculated that dAGEs are only partially absorbed, and those of with low molecular weight AGEs, do not interact with RAGE, though it has been proposed that could induce endogenous formation of high molecular weight AGEs.

AGE generation can also take place *in situ* in intestinal lumen, by means of fructose, high fructose corn syrup (HFCS), fruits or fruit juices, ingested along with protein-rich foods.

Until 1970, daily fructose intake was between 6 and 12 grams, mainly from fruits. Limited availability and soaring prices for saccharose motivated fructose utilization in gastronomy as an alternative to saccharose. Fructose intake has been rising consistently since 1980. HFCS is currently incorporated in soft drinks, pastry, canned fruits, marmalades and many other processed foods.

Surveys conducted in America[38] and Europe[39] have reported that one third of population have increased 25% its caloric intake in the form of carbohydrates, together with a reduction in nutrients. Caloric intake from simple sugars, glucose and fructose added to beverages and foods raised from 5% to 13% of total caloric intake. In soft drinks, fructose represents between 55% and 58% of total sugar content[40]. Fructose content is not easily evident for consumers since its presence is often expressed as “HFCS and/or sugar”.

Fructose does not require insulin for metabolim, and it is far more reactive than glucose and therefore, it is an important source of AGE generation.

Fat and muscle are the main glucose consumers. In presence of insulin deficit or resistance, glucose cannot be utilized, and other non-insulin-dependent tissues have high availability of intra- and extracellular glucose. High glucose levels generate elevated fructose levels.

Multiple observations reported between 2013 and 2017[41-44] make almost undeniable the pathogenic effects of high fructose intake, especially as HFCS, in generating AGEs. A caveat is therefore relevant: not only saccharose intake must be cut down, but also that of fructose, as much as possible, reducing daily consumption of fruits to 200 to 400 grams.

An *in vitro* study has reported that artificial non-saccharide sweeteners aspartame and sucralose induce glycation on human and bovine serum albumin, immunoglobulin G, and coagulation factors VIII and IX. This phenomenon could be related to the presence of glucose-like reactive groups that interact with amine groups in lysine. A more recent study has not confirmed these observations and has reported an anti-glycation effect for acesulfame potassium[45, 46].

Maillard Reaction By-products

Acrylamide and furan are by-products of Maillard reaction that can potentially increase in the long term the risk of cancer. Acrylamide may also convey potentially noxious effects, such as neurological damage and chromosome alterations. Several international agencies are promoting control measures of involved foods, including french fries, biscuits, pastry, instant coffee, chocolate and cereal-based additives for milk and yogurt (Food Standards Agency: Survey of acrylamide and furan in UK retail products, 2014-2018).

Glycation products are also denominated glycotoxins in view of their pathogenic effects. They participate in free radical generation, activate proinflammatory cytokines, and alter protein and nucleic acid chemical structure and function. Glycotoxins have clear pathogenic roles in diabetes and chronic kidney disease, and possibly in ageing and neurodegenerative diseases. Mitochondrial derangements give foundation to the metabolic theory of cancer, and Maillard reaction by-products potentially increase cancer risk.

Preserving Health

Human body is furnished with a vast array of antioxidant compounds to protect cells from glycation products. Several foods also provide antioxidant and anti-inflammatory substances, like retinol, ascorbic acid, tocopherol, flavonoids, lycopene, indoles, and luteins, contained in fruits, fresh vegetables, green tea, *yerba mate*, and wine.

There have been attempts in clinical nutrition to prevent generation of Amadori products and AGEs. Hydralazine derivatives are more reactive to amine groups than carbonyl[47]. Aminoguanidine has shown to be effective in preventing AGE formation and protein reticulation; these effects have been observed *in vitro* and *in vivo* in vascular connective tissue in rats[48].

AGE inhibitors are being evaluated for clinical use. Pyridoxamine has proved most effective. Several compounds, trace elements and herbs have a purported ability to decrease endogenous AGE damage, among them lipoic acid, carnitine, taurine, benfotiamine, α-tocopherol, niacinamide, pyridoxal, riboflavin, selenium, zinc, manganese, carnosine, catechin, quercetin, curcumin, sulforaphane, cinnamon, clove, oregano, garlic, ginger, tea, *yerba mate*, and chocolate[49, 50].

Research with alcoholic extracts of several spices, especially cinnamon, clove and black pepper, has shown these compounds are effective in reducing protein glycation, related to their content of flavonoids[51-53]. It has been suggested that these products can be added topically to foods before cooking, but confirmatory studies are still lacking.

Ilex paraguariensis, the *yerba mate*, has a potent antioxidant action, superior to green tea, and an inhibitory effect over AGE generation as potent as that of aminoguanidine; these effects are due to high content in *yerba mate* of two main phenolic compounds, chlorogenic acid and caffeic acid[54]. Still other polyphenols (naringin, ellagic acid) and isoflavones (genistein) have been studied regarding their protective effects against glycation[55].

Since recognition that HbA1c is the best parameter for diabetes treatment control, several observations in human and in animals have provided knowledge about the role of glycation in the pathogeny of chronic diseases, not related to diabetes. Experts think that preventive measures in dietary habits and lifestyle are warranted.

Cooking methods like boiling, steaming, poaching, stewing or microwaving are preferred, due to lesser temperatures, higher humidity and shorter exposure times, because they generate significantly less glycotoxins. Boiling and steaming reduce logarithmically dAGE generation[56]. Beef acidification with vinegar or lemon juice, one hour before oven or grill cooking, stewing or poaching, reduces glycotoxin generation. Overheating foods before consuming must be avoided.

Reduction in endogenous glycation is achieved mainly by glucose control. Foods with high glycemic index (high saccharose and fructose content) are to be avoided, to reduce glycemic

load. Daily consumption of 2 or 3 servings of fruit and raw vegetables, as well as spices like turmeric and ginger, provide adequate antioxidant intake.

In theory, antioxidant compounds like resveratrol, present in red wine, are effective in limiting production of oxygen reactive species that accelerate AGE generation[57]. Black chocolate content in flavonoids and polyphenols gives it antioxidant properties, reduces insulin resistance, lowers blood pressure and increases endothelial bioavailability of nitric oxide, reducing cardiovascular risk[58].

Prebiotics, probiotics, fiber and fermented foods are central in maintaining a healthy intestinal microbial flora. Microbiota biological contribution —microbiome— produces hydrolytic enzymes, required to antioxidant absorption and AGE and ALE sequestering. Lactobacilli may probably eliminate AGEs and ALEs from foods, as well as gluten and carcinogens[59].

Sport training can also reduce AGEs[60]. On the contrary, tobacco smokers show elevated levels in lens and blood vessels[61]. In animal models, caloric restriction reduces glycotoxin content in skin collagen[62].

In conclusion, reduced intake of certain foods (without complete banning them), eventually and not daily consumption, plus changes in lifestyle, can contribute successfully to health preservation (Table 1).

TABLE 1. Attenuating potential pathogenic effects of glycotoxins

Alimentary habits and lifestyle
- Prefer boiling water, steam or microwave for cooking
- Use lemon juice or vinegar acidification before grill, griddle or oven
- Avoid foods with high glycemic index
- Avoid sugar, glucose and fructose, especially processed foods and soft drinks
- Eat daily 2 or 3 portions of fresh vegetables and fruits
- Use preferently certain spices: turmeric, ginger, cinnamon, clove, black pepper
- Consume tea and *yerba mate*
- Drink red wine, one glass daily
- Exercise or make a sport 5 days a week

-	Limit alcohol consumption. Quit smoking
-	Avoid foods with low nutritional value end high caloric density

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