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Advanced Glycation End Products in Foods and a Practical Guide to Their Reduction in the Diet

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Abstract

Advanced glycation end products (AGEs), also known as glycotoxins, are a diverse group of highly oxidant compounds with pathogenic significance in diabetes and in several other chronic diseases (1–6). AGEs are created through a nonenzymatic reaction between reducing sugars and free amino groups of proteins, lipids, or nucleic acids. This reaction is also known as the Maillard or browning reaction (7). The formation of AGEs is a part of normal metabolism, but if excessively high levels of AGEs are reached in tissues and the circulation they can become pathogenic (2). The pathologic effects of AGEs are related to their ability to promote oxidative stress and inflammation by binding with cell surface receptors or cross-linking with body proteins, altering their structure and function (8–10). Among the better-studied AGEs are the stable and relatively inert N^{ε}-carboxymethyllysine (CML) and the highly reactive derivatives of methyl-glyoxal (MG). Both these AGEs can be derived from protein and lipid glycoxidation (11,12).

In addition to AGEs that form within the body, AGEs also exist in foods. AGEs are naturally present in uncooked animal-derived foods, and cooking results in the formation of new AGEs within these foods. In particular, grilling, broiling, roasting, searing, and frying propagate and accelerate new AGE formation (7,13). A wide variety of foods in modern diets are exposed to cooking or thermal processing for reasons of safety and convenience as well as to enhance flavor, color, and appearance. The fact that the modern diet is a large source of AGEs is now well-documented (3,7,13). Because it had previously been assumed that dietary AGEs (dAGEs) are poorly absorbed, their potential role in human health and disease was largely ignored. However, recent studies with the oral administration of a single AGE-rich meal to human beings as well as labeled single protein-AGEs or diets enriched with specific AGEs such as MG to mice clearly show that dAGEs are absorbed and contribute significantly to the body's AGE pool (14–16).

Consumption of AGE-rich diets by mice is associated with elevated circulating and tissue AGEs and conditions such as atherosclerosis (17) and kidney disease (18). On the other hand, restriction of dAGEs prevents vascular and kidney dysfunction (18,19), diabetes type 1 or type 2 (20), improves insulin sensitivity (21,22), and accelerates wound healing (23). Low dAGE intake has also been shown to lengthen lifespan to the same extent as does energy restriction in mice (16). Studies in healthy human beings show that dAGEs directly correlate with circulating AGEs, such as CML and MG, as well as with markers of oxidative stress (24). Moreover, restriction of dAGEs in patients with diabetes (25) or kidney disease (26,27) as well as in healthy subjects (28) also reduces markers of oxidative stress and inflammation. Together, the findings from animal and human studies suggest that avoidance of dAGEs in food helps delay chronic diseases and aging in animals and possibly in human beings (3).

From a practical perspective, aside from a few reports, which include an initial dAGE database on 249 foods (13), this area is void of relevant information and guidance for professionals. The purpose of this report is to expand the existing dAGE database by more than twofold, validate the methods used to test AGEs in food, examine different procedures and reagents on new dAGE formed, and introduce practical methods to reduce the consumption of dAGEs in daily life.

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METHODS

AGE Content of Foods

The AGE content of food samples was analyzed during the period 2003–2008. Foods were selected on the basis of their frequency on 3-day food records collected from healthy subjects in a catchment population in the Upper East Side and East Harlem in Manhattan, New York, NY. Therefore, these foods represent foods and culinary techniques typical of a Northeastern American multiethnic urban population. Foods were obtained from the cafeteria of The Mount Sinai Hospital, from local restaurants or supermarkets, or were prepared in the General Clinical Research Center at the Mount Sinai School of Medicine. Foods were subjected to standard cooking methods such as boiling (100°C), broiling (225°C), deep-frying (180°C), oven-frying (230°C), and roasting (177°C), unless otherwise stated in the database (see Table 1 available online at www.adajournal.org). The time of cooking varied as described in the database. Test procedures such as marinating, application of differing heating conditions, or cooking foods in differing fats or oils are also described in the database.

Table 1

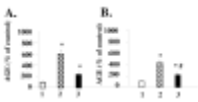
The advanced glycation end product (AGE) content of 549 foods, based on carboxymethyllysine content

Preparation of food samples for AGE measurement was performed as previously described (13). Briefly, food samples were homogenized and dissolved in phosphate buffer saline and the supernatants tested for AGEs with enzyme-linked immunosorbent assay based on a monoclonal anti-CML antibody (4G9) (29,30). The AGE content of each food item was based on the mean value of at least three measurements per sample and expressed as AGE kilounits/100 g food.

Selected items from different food categories were tested by a second enzyme-linked immunosorbent assay for content of MG-derivatives using an anti-MG monoclonal antibody (3D11 mAb) (29) and the results were expressed as nmol/100 g or nmol/100 mL food. The test sensitivity for CML and MG was 0.1 U/mL and 0.004 nmol/mL, respectively; the intra-assay variation was ±2.6% (CML) and ±2.8% (MG) and the inter-assay variation was ±4.1% (CML) and ±5.2% (MG).

AGE Inhibitory Agents

Because a low or acidic pH arrests AGE development, new AGE formation in cooked meat was tested following exposure to acidic solutions (marinades) of lemon juice and vinegar. Samples from lean beef were marinated in acidic solutions of either lemon or vinegar for 1 hour before cooking (see the Figure). In addition, the effect of a prototypic AGE inhibitor (aminoguanidine, 200 μmol/L) was compared to that of a lipid antioxidant (butylated hydroxytoluene [BHT], 100 μmol/L) on new AGE formation during heating by assessing CML content in oil (extra virgin olive oil, Colavita, Linden, NJ) samples, heated at 100°C for 5 minutes.



Figure

Effect of acidic environment on the advanced glycation end product (AGE) content of beef. Beef (25 g) was roasted for 15 minutes at 150°C with or without premarinating in 10 mL vinegar (A) or lemon juice (B) for 1 hour. Samples were homogenized **...**

Statistical Analysis

Data in the Table 1 (available online at www.adajournal.org), Table 2, and the Figure are presented as mean±standard error of the mean. Differences of mean values between groups were tested by unpaired Student *t* test or analysis of variance (followed by Bonferroni correction for multiple comparisons), depending on the number of groups. For nonparametric values, the Mann-Whitney U unpaired test or the Kruskal-Wallis analysis of ranks was used, depending on the number of groups. Correlation analyses were evaluated by Pearson's correlation coefficient. Significant differences were defined as a P value <0.05 and are based on two-sided tests. Data were analyzed using the SPSS statistical program (version 15.0 for Windows, 2005, SPSS Inc, Chicago, IL). For data presentation, food groups were based on the American Diabetes Association and the American Dietetic Association exchange lists for diabetes (31).

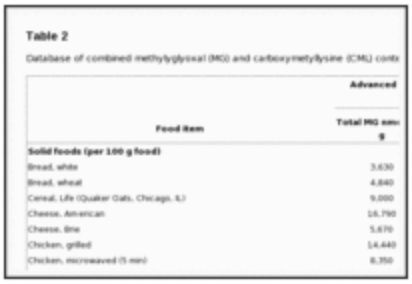


Table 2

Database of combined methylyglyoxal (MG) and carboxymetyllysine (CML) conte

Food item	Advanced Total MG mm g
Solid foods (per 100 g food)	
Bread, white	3,630
Bread, wheat	4,840
Cereal, Life (Quaker Oats, Chicago, IL)	9,000
Cheese, American	16,790
Cheese, Brie	5,670
Chicken, grilled	14,440
Chicken, microwaved (5 min)	8,350

Table 2

Database of combined methylyglyoxal (MG) and carboxymetyllysine (CML) content of selected foods

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RESULTS AND DISCUSSION

AGE Content of Foods as Determined by CML Levels

The AGE content in 549 foods, based on CML, is presented in Table 1 (available online at www.adajournal.org).

The new database contains more than twice the number of food items than the previously reported database (13) and shows that, based on standard serving sizes, the meat group contained the highest levels of AGEs. Although fats tend to contain more dAGE per gram of weight, meats will likely contribute more to overall dAGE intake because meats are served in larger portions than are fats. When items in the meat category prepared by similar methods were compared, the highest dAGE levels were observed in beef and cheeses followed by poultry, pork, fish, and eggs. Lamb ranked relatively low in dAGEs compared to other meats (Table 1 available online at www.adajournal.org). It is noteworthy that even lean red meats and poultry contain high levels of dAGEs when cooked under dry heat. This is attributable to the fact that among the intracellular components of lean muscle there exist highly reactive amino-lipids, as well as reducing sugars, such as fructose or glucose-6-phosphate, the combination of which in the presence of heat rapidly accelerates new dAGE formation (30,32).

Higher-fat and aged cheeses, such as full-fat American and Parmesan, contained more dAGEs than lower-fat cheeses, such as reduced-fat mozzarella, 2% milk cheddar, and cottage cheese. Whereas cooking is known to drive the generation of new AGEs in foods, it is interesting to note that even uncooked, animal-derived foods such as cheeses can contain large amounts of dAGEs. This is likely due to pasteurization and/or holding times at ambient room temperatures (eg, as in curing or aging processes) (33). Glycation-oxidation reactions, although at a slower rate, continue to occur over time even at cool temperatures, resulting in large accumulation of dAGEs in the long term.

High-fat spreads, including butter, cream cheese, margarine, and mayonnaise, were also among the foods highest in dAGEs, followed by oils and nuts. As with certain cheeses, butter and different types of oils are AGE-rich, even in their uncooked forms. This may be due to various extraction and purification procedures involving heat, in combination with air and dry conditions, however mild they are.

Of note, with heat kept constant, the type of cooking fat used led to different amounts of dAGEs. For instance, scrambled eggs prepared with a cooking spray, margarine, or oil had ~50% to 75% less dAGEs than if cooked with butter (Table 1 available online at www.adajournal.org).

In comparison to the meat and fat groups, the carbohydrate group generally contained lower amounts of AGEs (Table 1 available online at www.adajournal.org). This may be due to the often higher water content or higher level of antioxidants and vitamins in these foods, which may diminish new AGE formation. Furthermore, in this food category, most polysaccharides consist of non-reducing sugars, less likely to give rise to AGEs. The highest dAGE level per gram of food in this category was found in dry-heat processed foods such as crackers, chips, and cookies. This is likely due to the addition of ingredients such as butter, oil, cheese, eggs, and nuts, which during dry-heat processing substantially accelerate dAGE generation. Although AGEs in these snack types of food remain far below those present in meats, they may represent an important health hazard for people who consume multiple snacks during the day or as fast meals (34).

Grains, legumes, breads, vegetables, fruits, and milk were among the lowest items in dAGE, unless prepared with added fats. For instance, biscuits had more than 10 times the amount of dAGEs found in low-fat breads, rolls, or bagels.

Nonfat milk had significantly lower dAGEs than whole milk. Whereas heating increased the dAGE content of milk, the values were modest and remained low relative to those of cheeses (Table 1 available online at www.adajournal.org). Likewise, milk-related products with a high moisture index such as yogurt, pudding, and ice cream were also relatively low in AGEs. However, hot cocoa made from a dehydrated concentrate contained significantly higher amounts of AGEs.

AGE Content of Foods as Determined by MG Levels

Selected common foods were simultaneously analyzed for MG derivatives to determine whether food AGEs other than CML followed the same pattern (Table 2). A highly significant linear correlation (r=0.8, P=0.0001) was observed between the CML and MG content of foods prepared by different cooking techniques. As with CML, foods high in protein and fat contained higher amounts of MG than did carbohydrate-rich foods. Noncooked butter and oil contained low amounts of MG, but in dry-heated fat, as in french fries, MG content was significantly higher (Table 2). The highly significant internal correlation between two chemically distinct AGEs (CML and MG) in a variety of foods prepared by different methods validates the methodology applied and supports the choice of CML levels as a useful marker of dAGE content.

Effect of Cooking Procedures on AGE Formation in Foods

Preparation of common foods under varying conditions of water and heat had a different effect on dAGE content. For example, scrambled eggs prepared in an open pan over medium-low heat had about one half the dAGEs of eggs prepared in the same way but over high heat. Poached or steamed chicken had less than one fourth the dAGEs of roasted or broiled chicken. In all food categories, exposure to higher temperatures and lower moisture levels coincided with higher dAGE levels for equal weight of food as compared to foods prepared at lower temperatures or with more moisture. Thus, frying, broiling, grilling, and roasting yielded more dAGEs compared

to boiling, poaching, stewing, and steaming. Microwaving did not raise dAGE content to the same extent as other dry heat cooking methods for the relatively short cooking times (6 minutes or less) that were tested.

Effect of AGE Inhibitors on New AGE Formation in Foods

The heat-induced new AGE formation in olive oil was completely prevented in the presence of the AGE inhibitor, aminoguanidine, but only partly blocked by the anti-oxidant BHT (Table 2). The amelioration of new AGE formation by the AGE inhibitor aminoguanidine compared to the anti-oxidant BHT suggests that the process seems to be driven by glycation rather than oxidation.

New AGE formation in cooked meat was also inhibited following exposure to acidic solutions (marinades) of lemon juice and vinegar. Beef that was marinated for 1 hour in these solutions formed less than half the amount of AGEs during cooking than the untreated samples (Figure).

Implications for Practice

Currently, there are limited data on dAGE intakes in the general population. The average dAGE intake in a cohort of healthy adults from the New York City area was recently found to be 14,700±680 AGE kU/day (24). These data could tentatively be used to define a high- or low-AGE diet, depending on whether the estimated daily AGE intake is significantly greater or less than 15,000 kU AGE. From the data presented in Table 1 (available online at www.adajournal.org), it is easy to see how people who consume a diet rich in grilled or roasted meats, fats, and highly processed foods could achieve a dAGE intake in excess of 20,000 kU/day. Conversely, people who regularly consume lower-meat meals prepared with moist heat (such as soups and stews) as part of a diet rich in plant foods could realistically consume half the daily intake seen in this cohort. A safe and optimal dAGE intake for the purposes of disease prevention has yet to be established. However, in animal studies, a reduction of dAGE by 50% of usual intake is associated with reduced levels of oxidative stress, less deterioration of insulin sensitivity and kidney function with age, and longer life span (16).

Reducing dAGE may be especially important for people with diabetes, who generate more endogenous AGEs than those without diabetes (5) and for those with renal disease, who have impaired AGE clearance from the body (14). Recently there has been heightened interest in therapeutic diets that are higher in protein and fat and lower in carbohydrate for weight loss, diabetes, and cardiovascular disease (35–41). This type of dietary pattern may substantially raise dAGE intake and thus contribute to health problems over the long term.

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CONCLUSIONS

AGEs in the diet represent pathogenic compounds that have been linked to the induction and progression of many chronic diseases. This report reinforces previous observations that high temperature and low moisture consistently and strongly drive AGE formation in foods, whereas comparatively brief heating time, low temperatures, high moisture, and/or pre-exposure to an acidified environment are effective strategies to limit new AGE formation in food (13). The potentially negative effects of traditional forms of cooking and food processing have typically

remained outside the realm of health considerations. However, accumulation of AGEs due to the systematic heating and processing of foods offers a new explanation for the adverse health effects associated with the Western diet, reaching beyond the question of over-nutrition.

The current dAGE database demonstrates that a significantly reduced intake of dAGEs can be achieved by increasing the consumption of fish, legumes, low-fat milk products, vegetables, fruits, and whole grains and by reducing intake of solid fats, fatty meats, full-fat dairy products, and highly processed foods. These guidelines are consistent with recommendations by organizations such as the American Heart Association (42), the American Institute for Cancer Research (43), and the American Diabetes Association (44). It should, therefore, be possible to integrate this new evidence into established guidelines for disease prevention as well as medical nutrition therapy for a wide variety of conditions.

Equally important, consumers can be educated about low-AGE–generating cooking methods such as poaching, steaming, stewing, and boiling. For example, the high AGE content of broiled chicken (5,828 kU/100 g) and broiled beef (5,963 kU/100 g) can be significantly reduced (1,124 kU/100 g and 2,230 kU/100 g, respectively) when the same piece of meat is either boiled or stewed. The use of acidic marinades, such as lemon juice and vinegar, before cooking can also be encouraged to limit dAGE generation. These culinary techniques have long been featured in Mediterranean, Asian, and other cuisines throughout the world to create palatable, easily prepared dishes.

The new database may have limitations, including the fact that foods were selected from diets common in a northeastern metropolitan US area, and may thus not represent the national average. Another limitation is that only two of many AGEs have been measured. However, the fact that both are associated with markers of disease in healthy subjects and are elevated in patients with diabetes and kidney disease lends credibility to their role as pathogens in foods consumed by the general public and persons with certain chronic diseases.

Ongoing studies are needed to further expand the dAGE database and investigate additional methods for reducing AGE generation during home cooking and food processing. Future studies should continue to investigate the health effects of AGEs and refine recommendations for safe dietary intakes. However, current data support the need for a paradigm shift that acknowledges that how we prepare and process food may be equally important as nutrient composition.

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