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Review Article

Advanced Glycosylation End Products: Effects in Chronic Kidney Disease and Related Disorders

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ABSTRACT

Chronic kidney disease (CKD) is a clinical condition that can end in end-stage renal disease (ESRD) and needs dialysis or a kidney transplant. Hypertension, diabetes, obesity, and cardiovascular risk factors are the main contributing factors to the CKD process. One of the factors with exogenous and endogenous sources affecting the CKD progression or prognosis and its complications is the accumulation of advanced glycosylation end products (AGEs) through the glycosylation of proteins, lipids, or nucleic acids or by dietary sources. AGEs accumulation can adversely affect the long-term complications of diabetic patients such as nephropathy or retinopathy, especially in those with type 2 diabetes. These compounds can affect cardiovascular health by inducing cardiomyopathy and congestive heart failure. Dialysis patients are among those with higher oxidative stress and lipid peroxidation which can affect the levels of AGEs in these patients. Lower clearance or excretion of the AGEs through kidneys and higher dietary absorption can cause higher levels of AGEs in this population. Higher AGEs are accompanied by higher rates of CVD, connective tissue disorders, mortality and lower quality of life in CKD patients. Dietary modifications are considered one of the main factors affecting the levels of AGEs in CKD patients which can improve their prognosis and complications even in the absence of diabetes. The ways of cooking and the ingredients focusing on reducing the temperature, cooking time, moist heat, and using acidic ingredients such as lemon juice or using anti-AGE compounds are recommended for reducing AGEs formation in foods.

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Introduction

Chronic kidney disease (CKD) is recognized as an important public health problem. It can be diagnosed by biochemical tests including a creatinine-based estimate of the glomerular filtration rate (GFR) (1) Ęr. CKD is a dangerous clinical condition because renal impairment may prelude to end-stage renal disease (ESRD), and in this disease stage, renal replacement therapy (dialysis or transplantation) is needed (2, 3). Approximately 90% of patients diagnosed with ESRD received maintenance hemodialysis (HD) treatment (4).

Also, the risk for cardiovascular diseases is higher in patients with ESRD (5). Hypertension, diabetes, and obesity are recognized as the main risk factors of CKD at the population level (6, 7). One of the main factors affecting the complications, morbidity, mortality, and poor prognosis in CKD patients and related disorders is the accumulation of the products called advanced glycosylation end products (AGEs) which can be produced endogenously or obtained exogenously through diet.

Advanced Glycation End Products

Advanced glycosylation end (AGE) products are heterogeneous group of compounds derived from non-enzymatic glycosylation of proteins, lipids, and nuclear acids through complex and sequential reactions known as the Maillard reaction (8). Although a limited formation of AGE is a part of normal metabolism, studies over the past century have characterized the detrimental effects of excess accumulation of these glycotoxins in nearly every organ system, including diabetes, neurodegenerative diseases, chronic pulmonary diseases, and rheumatologic illnesses (9).

Exogenous and Diet-derived AGEs

Animal and human-based studies showed that along with the endogenous production of AGEs in the body, exogenous AGEs could be found naturally in many foods and tobacco. On the other hand, many methods of processing can cause AGE formation in the foods. They are in the foods that are cooked at high temperatures, especially animal-derived products that are rich in protein and fat. Indeed, some of the cooking methods including barbecuing, grilling, roasting, and frying may contribute to the higher dietary AGEs (10). Some foods have higher amounts of AGE per serving and their consumption should be limited (Table 1) (11).

Most common AGEs

Pentosidine is a fluorescent glycoxidation product that is isolated by Sell and Monnier, as the commonly known AGEs. It can be formed by cross-linking the glucose, fructose, or ascorbate to an arginine and a lysine residue (12). Carboxymethyl-lysine (CML) also known as N (epsilon)-(carboxymethyl) lysine is a well-characterized and non-fluorescent AGE that was first described by Ahmed in 1985. The CML is formed by the oxidation of fructosyl-lysine as an Amadori product or by a reaction of glyoxal with the amino group of lysine. It is the most prevalent marker for AGE concentration analysis in foods (13).

AGEs in Disorders

AGEs affect nearly every type of cell and molecule in the body, which have a pathogenic role in some conditions that causes intracellular damage and apoptosis. Recent studies working on the treatment and prevention of related complications to some disorders including aging, coronary artery disease, kidney failure, Alzheimer's disease, osteoarthritis, and diabetes, demonstrated that most of the complications especially in diabetic patients were due to the accumulation of AGEs (14). Chronic disorders are significantly associated with oxidative stress in humans and animals, as decreased expression of antioxidative enzymes along with NADPH oxidase activation could contribute to the high production of reactive oxygen species (ROS) in the tissues. Activation of nuclear factor (NF)-κB, and JNK pathways are accompanied by obesity, a high-fat diet, and cellular stresses, which can increase inflammatory responses in body tissues. Some ligands including TNFR, IL-1R, and RAGE that are receptors for tumor necrosis factor alpha (TNF-α), interleukin-1 (IL-1), and AGEs can also activate the JNK pathway during metabolic dysregulation (15).

Plasma AGEs in Chronic Kidney Disease: Clinical Implications

Galli *et al.* showed progressively higher levels of plasma pentosidine, by using high-performance liquid chromatography comparing matched groups of healthy controls, CKD, and HD patients, respectively. Within the HD group, a negative correlation existed between the level of plasma pentosidine and dialysis frequency. They also proved that protein-leaking HD reduced the level of plasma pentosidine. In renal transplantation patients, plasma pentosidine levels were similar to those in healthy controls (16).

Galli's data are in line with those of other groups, showing that AGEs indeed are accumulated in non-diabetic uremic patients, despite their normal serum glucose levels. In lower CKD classes, a relationship between AGE levels [Nε-carboxymethyl-lysine (CML)] and renal function was also evident, both in selected groups and in the community (17). Among dialysis patients, both diabetics and non-diabetics have high plasma pentosidine and CML levels. Unfortunately, current HD techniques are only able to clear a portion of AGE from plasma (18). Hou *et al.* proposed that AGE and RAGE might contribute to the amplification of inflammation in non-diabetic CKD (19). Further, Uribarri *et al.* showed that AGE intake contributed to the level of plasma AGE levels in CKD patients (20).

AGEs Accumulation and Cardiovascular Risks: Clinical Implications

There is a potential association between AGEs

Table 1: Advanced glycosylation end products content of selected foods per serving (11).

Food item	Serving (g)	AGE (kU/serving)
Peanut butter, smooth	30	2255
Walnut, roasted	30	2366
Soybeans, roasted and salted	30	500
Mayonnaise	5	470
Cashews, roasted	30	2942
Avocado	30	473
Almond, roasted	30	1995
Olive, ripe, large (5g)	30	501
Sunflower seeds, roasted and salted	30	1408
Sunflower seeds, roasted and salted	5	876
Canola oil	5	451
Corn oil	5	120
Olive oil	5	595
Oil, olive, extra virgin, first cold pressed	5	502
Safflower oil	5	151
sesame oil	5	1084
Sunflower oil	5	197
Cottonseed oil	5	426
Beef, roast	90	5464
Chicken breast, roasted with skin	90	5975
Lamb leg, boiled for 30 min	90	1096
Shrimp, fried	90	3895
Tuna, canned	90	1566
Salmon, pan-fried in olive oil	90	2775
Cheddar Cheese	30	1657
Feta cheese	30	2527
Mozzarella cheese, reduced fat	30	503
Fried egg	45	1237
Egg, omelet	30	49
Biscuit	30	441
Vanilla cookie	30	966
White sugar	5	0
Whole wheat bread, slice	30	31
Potato, homemade French fries	100	694
Canned corn	100	20
Banana	100	9
Carrot	100	10
Grilled eggplant	100	256
Whole milk (4%)	250	12
Fat-free milk	250	1
Fat-free milk, microwaved for 3 min	250	86
Honey	15	1
Ice cream, cone	30	46
Hummus	100	701
Macaroni and cheese, baked	100	4070

AGE: advanced glycosylation end product

accumulation and congestive heart failure (CHF) due to various reasons. Diastolic dysfunction and heart failure are most common among those with AGEs accumulation, including those afflicted with diabetes and chronic renal failure (CRF). AGEs could possibly engage in the pathogenesis of cardiomyopathy in diabetic patients (21). There are two mechanisms concerning the AGEs' effects on the pathogenesis of heart failure. AGEs could interfere with the matrix proteins including elastin, collagen, and laminin, and this can induce fibrosis and change the elasticity turnover (21, 22). Another mechanism is pertinent to the interactions of AGE-RAGE which can cause many changes in the myocardium and vascular system that can negatively affect heart metabolism, especially calcium metabolism (23, 24). On the other

hand, AGEs accumulation can cause endothelial dysfunction, higher thrombogenicity, and increase risk of atherosclerosis that can all end in coronary heart diseases. As another mechanism, it can be mentioned that hypo-perfusion and hypo-function of the kidney which can happen in those with heart failure could increase the level of AGEs due to the lower clearance and this can affect the pathogenesis of CHF (25).

It was confirmed that using the drug named Alagebrium (ALT-711) which is an AGEs cross-link breaker could improve the left ventricular mass. Diabetic patients with CHD had higher levels of AGEs when compared to those only afflicted with diabetes (26). It is hypothesized that the plasma concentration of AGEs is associated with the severity of CHF, however, the tissue concentration of AGEs can directly show the cross-linking of intracellular proteins and their interactions with receptors (21). Moreover, AGEs accumulation was highly associated with collagen-specific fluorescence in the skin, aortic plaques, and myocardium in diabetic patients (27).

AGEs Accumulation in Diabetic Patients and the Progression of Nephropathy: Clinical Implications

Diabetic patients have higher levels of AGEs than non-diabetic ones due to the hyperglycemia in these patients. AGEs have potential effects on the macro and microvascular complications of diabetic patients. Higher tissue levels of AGEs, serum levels of HBA1C, and fructoseamine biomarkers can confirm the association between AGEs and hyperglycemia (28, 29). Increased levels of AGEs were reported in type 1 and 2 diabetes and it could increase in the early stages of the disease up to almost 1.5 folds. AGEs accumulation is associated with diabetes complications including retinopathy, nephropathy, and coronary heart disease (CHD) in type 2 diabetic patients (30).

Skin autofluorescence (AF) is an index for measuring the level of AGEs in the tissues, showing the extent of oxidative and glycemic stress (31). It was reported that skin AF was associated with microvascular complications in diabetic patients (30). Skin AF was strongly associated with disease duration, HbA1c, plasma creatinine, albumin to creatinine ratio, and HDL-cholesterol (31). In a study by Lutgers and colleagues, it was asserted that skin AF is an important marker for microvascular complications, even in controlled type 2 diabetic patients (32). Further, it was mentioned that AGEs were considered causing factors in the progression of nephropathy in diabetics (33). It seems that the severity of nephropathy is pertinent to the accumulation of AGEs. Early symptoms of renal diseases are correlated with AGEs aggregation in diabetic patients (34).

AGEs Accumulation in ESRD Patients: Clinical Implications

AGE accumulation happens in the collagen and plasma of normoglycaemic patients with uremia. This implies that the abnormality doesn't happen only due to the glycation of proteins and the possible stages are as follows: (i) ESRD patients encounter a high level of oxidative stress (35) and many factors such as inflammation (36), bioincompatability of dialysis membrane, infection, and lower antioxidant capacity can enhance this condition (37). ESRD patients experience higher levels of oxidative stress and lipid peroxidation and lower antioxidant activity due to the decreased levels of glutathione (38), even before starting dialysis (39). CKD patients, especially dialysis patients experience higher degrees of metabolic stress (40). (ii) The process of sugar and lipid oxidation that can generate carbonyl stress or decrease the carbonyl compound detoxification such as aldose reductase or glyoxalase 1 can happen in these patients (41). (iii) Moreover, renal excretion of AGEs can decrease because of a lower GFR and this can induce the accumulation of AGEs and lower tubular catabolism. Despite the conservation of kidney function in the early stages of CKD, tubular aggregation of AGEs can be seen in these patients before any severe nephron loss (41). (iv) On the other hand, due to the metabolic burden caused by insulin resistance or lower lipid clearance, de novo synthesis of AGEs can also happen (42).

Therefore, High levels of AGEs can be seen in ESRD patients and this can impair renal clearance and increase AGEs production. However, diet can potentially affect AGEs accumulation as an important source of exogenous AGE. The AGEs derived from dietary sources can sustain the circulating levels especially in the inflammatory and oxidative condition of CKD and in dialysis patients (43). Hence, dietary AGEs are important contributors to serum AGEs in patients with renal diseases. It was reported that dietary limitation of AGEs could happen safely, as there was no association between the dietary intakes of AGEs and protein, fat, and carbohydrate (20). Dietary restriction of AGEs can decrease kidney lesions in aging too. In addition, dietary changes with an emphasis on cutting down the AGEs content of the diet can improve the quality of life in patients with CKD (44).

Effects of AGEs on tissue damage and complications are those mechanisms focusing on the effects of AGEs on the progression of atherosclerosis and CHF, even in patients with non-renal diseases.

Hence, heart diseases are higher in CKD patients and are correlated with many dysfunctions in these patients. They can clearly increase the mortality rate in these populations (45). Therefore, assessing AGEs accumulation in CKD patients is critically important. It was asserted that skin AF was a potent determinant of survival in hemodialysis patients independent of other potential risk factors. It was mentioned that skin AF was a more important risk factor for mortality than the other risk factors including lipid profile or smoking, especially for cardiovascular mortality. However, the association between serum AGEs and survival is not clearly defined in hemodialysis patients, since measuring serum levels of AGEs is difficult and needs special methods (38). On the other hand, many factors can affect the AGE levels such as dialysis timing, dietary absorption, and smoking (46, 47). Skin AF, but not serum levels of AGEs, can also affect cardiovascular deaths or events in hemodialysis patients (21).

Despite the association between AGEs accumulation and cardiovascular mortality in CKD patients, further studies are recommended to assess this relationship. Some connective tissue disorders such as carpal tunnel syndrome or lytic bone cysts can also affect the prognosis in CKD patients. One of the main contributors to these disorders in ESRD patients is the accumulation of amyloid aggregates (48, 49). However, serum accumulation of AGEs can happen in CKD patients with connective tissue disorders and higher levels of AGEs were found on collagen samples of CKD patients with carpal tunnel syndrome even in the absence of amyloid deposits (50), showing the importance of AGE accumulation in the progression of connective tissue disorders in CKD patients.

Reducing AGEs through Dietary Modifications

Higher amounts of AGEs are produced through dry heat when compared to uncooked foodstuffs (10 to 100 folds higher levels). Animal foods that are high in protein and fat are highly rich in AGEs and new AGE production would possibly happen in these foods via the cooking process. However, carbohydrate-rich foods including fruits, vegetables, milk, and whole grains contain lower levels of AGEs. One of the ways for preventing the formation of AGE during cooking is the use of AGE inhibitory compounds such as aminoguanidine. On the other hand, cooking with moist heat or in shorter times or lower temperatures can prevent or reduce AGE formation during cooking. Using acidic ingredients including lemon juice or vinegar can also decrease the chance of AGE formation or decrease the level of this compound during cooking (11).

Conclusion

Advanced glycosylation end (AGE) products are the compounds produced by the non-enzymatic glycosylation of proteins, lipids, and nuclear acids through complex reactions known as the Maillard reaction or they can be obtained through dietary sources. AGES may have a vital role in the normal aging process and in the evolution of the complications of diabetes, CHD, and CKD. They have been implicated in the pathogenesis of cardiomyopathy and long-term complications in diabetes such as nephropathy and retinopathy. AGEs accumulation is increased in patients with ESRD and could affect the prognosis and complications of ESRD. Lower clearance of AGEs and higher dietary absorption of these compounds could cause AGE accumulation in CKD patients and dietary modification can be an appropriate way of managing high levels of AGEs in this population.

AGEs accumulation was proved to be a strong and independent determinant of total and cardiovascular morbidity and mortality, both in patients on dialysis and in diabetic patients. Assessment of AGEs accumulation may facilitate treatment management and further identify patients at risk of long-term complications. Regarding the dietary changes for preventing AGE formation, the ways of cooking and the ingredients focusing on reducing the temperature, cooking time, moist heat, and using acidic ingredients such as lemon juice or using anti-AGE compounds are recommended.

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Conflict of Interest

None declared.

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