Glucose degradation products (GDPs) are highly reactive precursors of advanced glycation end-products (AGEs). High glucose concentrations, GDPs, and AGEs can activate specific pathways, including inflammatory and oxidative stress response pathways, which may adversely affect the cardiovascular system. This review discusses the impact and possible mechanisms of action of GDPs and AGEs with regard to cardiovascular toxicity in chronic kidney disease patients. The AGE–RAGE pathway appears to be particularly important in the pathogenesis of cardiovascular diseases in dialysis patients. In the absence of definitive proof from randomized controlled trials, mounting evidence suggests that high levels of GDPs and AGEs play a role in the pathophysiology of cardiotoxicity.

Key words
Advanced glycation end-products, glucose degradation products, cardiotoxicity, cardiovascular toxicity, chronic kidney disease

Introduction
This overview of glucose degradation products (GDPs) and advanced glycation end-products (AGEs) discusses the impact of these substances on inflammatory and oxidative stress responses and on cardiovascular toxicity in dialysis patients.

Discussion

GDPs and AGEs
The GDPs are alkenes and aldehydes (1) and, as such, are highly reactive because of the electrons carried in the carbonyl group. A variety of GDPs can form in peritoneal dialysis (PD) solutions during heat sterilization or over long storage periods. The GDPs commonly found in PD solutions include glucosone, 3-deoxyglucosone (3-DG), 3,4-dideoxyglucosone-3-ene, 5-hydroxymethylfurfural, carboxymethyllysine (CML), formaldehyde, acetaldehyde, and methylglyoxal (MGO).

The GDPs and AGEs can potentially cause permanent structural and functional damage to proteins and cell tissues. They have been shown to inhibit cell proliferation, retard wound healing, induce apoptosis (programmed cell death), downregulate various cytokines, and inhibit respiratory burst in vitro (2–5). The release of various cytokines and chemokines from macrophages and lymphocytes can affect inflammatory responses, and respiratory burst is a crucial component of phagocytic defense reactions. Animal studies have shown that GDPs affect fibrosis, thickening of the peritoneal membrane, and peritoneal transport characteristics (6,7). The GDPs are also known to be precursors of AGEs. The AGEs result from spontaneous, nonenzymatic binding of carbohydrates to proteins or lipids, and AGE formation is increased by oxidative and carbonyl stress, which is common in patients with chronic renal failure (8).

GDPs and AGEs induce proinflammatory response and oxidative stress
The presence of high glucose concentrations, GDPs, and AGEs has been shown to activate specific pathways within cells that result in inflammatory and oxidative stress responses that can adversely affect the cardiovascular and renal systems (9). At a cellular level, high glucose concentrations and GDPs induce a proinflammatory response and oxidative stress either directly through increased mitochondrial activity, stimulation of protein kinase C, NADPH oxidase, or the polyol pathway. Alternatively, GDPs act through AGE formation and activation of the receptor for AGE (RAGE). The downstream result of this cascade is an excessive increase in reactive oxygen species and reactive nitrogen species that occurs through activation of proinflammatory pathways (for example, CDC42/Rac, MAPK, PI3K/AKT, JAK/STAT).
pro-atherogenic transcription factors (for example, nuclear factor κB), and pro-atherogenic adhesion molecules (for example, vascular cell adhesion molecule 1, intercellular adhesion molecule 1, E-selectin, tissue factor, endothelin).

The same mechanisms could also be at work in mesothelial cells. Welten et al. examined the kinetics of uptake by mesothelial cells of highly purified GDP species (MGO and 3-DG) and the resulting effects on various biologic and immunologic parameters (10). Results from enzyme-linked immunosorbent assays showed increased expression of vascular cell adhesion molecule 1 by MGO and 3-DG, and also production of interleukins 6 and 8 after exposure to 3-DG. In addition, incubation of mesothelial cells with MGO and 3-DG induced apoptosis and reduced proliferation.

Other GDP- and AGE-induced proinflammatory responses include the secretion of inflammatory cytokines and chemokines, monocyte chemotaxis, aggregation of platelets, activation of vascular endothelial and platelet-derived growth factor, quenching of nitric oxide activity, and inhibition of antibacterial activity (11,12).

**GDPs in PD solutions**

Conventional PD solutions have high levels of GDPs, in particular 3,4-dideoxyglucosone-3-ene, which is one of the most toxic GDPs (13,14). New PD solutions, with substantially lower levels of GDPs, have been developed because it was shown that it was GDP content, and not glucose, that primarily affected the biocompatibility of PD solutions (15–17).

Clinically, long-term exposure to GDPs in PD solutions, directly or through the generation of systemic AGEs, has been associated with infusion pain, impaired peritoneal host defenses, impairment of the peritoneal membrane, membrane permeability change, vascular disease, inflammation and oxidation, ultrafiltration failure, and cardiovascular toxicity (18,19). Such exposure could also significantly contribute to technique failure (20). It is therefore important to minimize the GDP content in PD solutions.

Several studies have assessed the biocompatibility of conventional compared with low-GDP PD solutions. In 2003, Zeier et al. reported a study designed to measure GDP absorption and increases in systemic AGE concentrations (19). Their results demonstrated that MGO disappears completely from dialysate as early as 2 hours after intraperitoneal instillation. In addition, plasma AGE concentrations (fluorescence and plasma CML concentration) were significantly higher after treatment with conventional PD solutions than with low-GDP solutions. The randomized multicenter Euro-Balance crossover trial indicated that, compared with use of conventional solutions, use of biocompatible solutions for PD resulted in better preservation of residual renal function as determined by increased urine volume and urine creatinine clearance. Further, that study clearly showed significantly lower concentrations of circulating AGEs when the low-GDP solution was used (21). The foregoing studies showed that GDPs from PD solutions are absorbed and contribute to increased systemic AGE levels, which means that they could potentially cause toxic effects through the proinflammatory and pro-atherogenic mechanisms described earlier.

**GDPs, AGEs, and RAGE in cardiotoxicity and chronic kidney disease**

Cardiovascular complications are the major cause of mortality in patients with chronic kidney disease (CKD), accounting for 50% of all deaths and being associated with an overall mortality risk about 30 times that seen in the general population (22). In the absence of definitive proof from randomized clinical trials, the impact of GDPs and AGEs on cardiovascular mortality in PD patients is still controversial (23). However, accumulating data from in vitro, in vivo, and clinical studies have suggested a causal role of GDPs and AGEs in cardiotoxicity.

Müller–Krebs et al. subjected Sprague–Dawley rats to 5/6 nephrectomy; a treatment group then received GDP infusions over a 4-week period, and a control group received no treatment (24). The authors found a significant increase in the levels of AGEs (as determined by CML expression in the myocardium and aorta), higher oxidative stress, and increased apoptosis in the treated group. They concluded that systemic GDPs can cause toxicity in cardiovascular tissues. The AGEs (specifically CML and pentosidine) were also detectable by immunohistochemistry in the fatty streaks and proliferative intima of arteries from patients with diabetic nephropathy (25) and in the intramyocardial blood vessels of patients who experienced a myocardial infarction (26). The staining patterns for AGEs have also been shown to correspond with protein carbonyl biomarkers of oxidative protein
GDPs, AGEs, and Cardiotoxicity

24

In addition to GDPs and AGEs, RAGE also seems to have a direct role in promoting cardiotoxicity. The receptor for AGE has been described as accumulating in hyperglycemic conditions (29). Subsequent studies showed that other molecules also bind to RAGE (for example, S100/calgranulins, amphoterin, and amyloid β peptide) and that upregulation of RAGE is associated with tissue injury (30–34), implicating RAGE and AGEs in the pathogenesis of multiple chronic disease states such as diabetes, immune and inflammatory foci, and neurodegenerative disorders. Furthermore, RAGE was also shown to modulate cardiac hypertrophy, apoptosis, and remodeling after infarction (35). In 2006, Bucciarrelli et al. (36) showed increased AGE immunoreactivity (CML, \( p < 0.03 \)) in rat and mouse hearts subjected to ischemia and reperfusion injury; hearts treated with soluble RAGE antagonist showed decreased AGE levels (MGO, \( p < 0.02 \)). The authors suggested a key role for RAGE in ischemic myocardial injury.

In a prospective cohort study in 2009, Semba et al. (37) investigated all-cause and cardiovascular mortality in 1013 patients who were 65 years of age or older. Over a 6-year period, 46.3% died from CVD, and patients within the highest tertile of CML were at higher risk of all-cause and CVD mortality [hazard ratio (HR) for all-cause mortality: 1.84; 95% confidence interval (CI): 1.3 to 2.6; HR for CVD mortality: 2.11; 95% CI: 1.3 to 3.5].

The AGE levels in arterial tissues were shown to be higher in dialysis patients than in healthy subjects (25), and accumulation of AGEs in hemodialysis (HD) patients may be an important contributor to the development of CVD (38). Thus, AGEs may provide a plausible link between CKD and cardiovascular toxicity (Figure 1). Several studies have demonstrated that tissue accumulation of AGEs, assessed by skin autofluorescence, can predict cardiovascular mortality in patients with CKD (39–41). Using univariate and multivariate analyses to investigate atherosclerosis associations in 54 HD patients, Nagano et al. (42) determined that skin levels of AGEs significantly correlated with high-sensitivity C-reactive protein. The authors concluded that tissue levels of AGEs and high-sensitivity C-reactive protein could have synergistic effects on the progression of atherosclerosis in HD subjects.

Summary

The GDPs are precursors of AGEs, and both products are cytotoxic. The generation of GDPs and AGEs has been associated with increased oxidative stress and inflammatory responses through the production of cytokines, chemokines, reactive oxygen species, reactive nitrogen species, pro-atherogenic transcription factors, and adhesion molecules. Evidence indicates that GDPs can directly induce toxicity in the myocardium and aorta. The AGE–RAGE axis has been implicated in the pathogenesis of CVDs in dialysis patients, including cardiac dysfunction from ischemic myocardial injury. In the absence of definitive proof from randomized controlled trials, mounting evidence seems to suggest that high levels of GDPs and AGEs play a role in the pathophysiology of cardiotoxicity.

Disclosures

All authors are full-time employees of Fresenius Medical Care North America, Waltham, Massachusetts, U.S.A.

References


10 Welten AG, Schalkwijk CG, ter Wee PM, Meijer S, van den Born J, Beelen RJ. Single exposure of mesothelial cells to glucose degradation products (GDPs) yields early advanced glycation end-products (AGEs) and a proinflammatory response. Perit Dial Int 2003;23:213–21.


26 Baidoshvili A, Krijnen PA, Kupreishvili K, et al. Nε-(carboxymethyl)lysine depositions in intramyocardial blood vessels in human and rat acute myocardial


Corresponding author:
Jose A. Diaz-Buxo, MD FACP, 309 East Morehead Street, Suite 285, Charlotte, North Carolina  28202 U.S.A.
E-mail: jose.diaz-buxo@fmc-na.com