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Amadori-Modified Glycated Serum Proteins and Accelerated Atherosclerosis in Diabetes: Pathogenic and Therapeutic Implications

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Diabetes confers a four-fold risk for atherosclerotic cardiovascular disease, manifest in the vessel wall as intimal thickening, smooth muscle hypertrophy, lipid accumulation, extracellular matrix expansion, and inflammatory cell infiltration (1). Although the exact mechanisms responsible for the accelerated atherosclerosis that occurs in patients with diabetes are incompletely defined, evidence is accumulating that Amadori-modified glycated serum proteins may play a substantive role. Numerous studies have indicated that serum proteins containing Amadori glucose adducts, which arise from the nonenzymatic condensation reaction between reducing sugar and susceptible amino groups that is increased in the diabetic state, acquire biologic properties that are strongly linked to the pathogenesis of vascular complications of diabetes. The Amadori-modification is structurally distinct from those associated with Advanced Glycation Endproducts (AGE), which arise from subsequent oxidation, degradation and other spontaneous reactions and which also are implicated in the development of long-term sequelae of diabetes. Additionally, Amadori-modified proteins operate through receptors different from RAGE, the receptors mediating biologic effects of AGE. This review focuses on proatherogenic properties of Amadori-modified serum proteins, which are perhaps underappreciated contributors to atherosclerosis in diabetes. Although the diabetic state promotes the Amadori-modification of many circulating proteins (2), giving rise to concentrations of glycated proteins approximately one and a half to three times those found in non-diabetic individuals that reflect integrated glycemia to which the protein has been exposed during its residence time in the circulation, information on glycation-induced functional alterations and potential pathophysiologic consequences is most extensive regarding the major plasma constituents albumin and lipoproteins. In the discussion that follows, the terms glycated albumin and glycated lipoprotein, unless otherwise defined, refer to the Amadori constructs.

Albumin

Glycated albumin exhibits potential atherogenic effects in various cell types, including mesangial, monocyte-macrophage, mesothelial, endothelial, and vascular smooth muscle cells. In monocyte-macrophages, precursors to atherosclerotic foam cells through processes involving adhesion, chemokine-directed migration, and receptor-mediated internalization of LDL particles (1,3–7), glycated albumin in concentrations simulating those found in clinical

specimens induces oxidative stress, promotes phosphorylation of Extracellular Signal Regulated Kinase (ERK), and increases Transforming Growth Factor (TGF)- β 1 production and nuclear translocation of the transcription factors Nuclear Factor (NF)- κ B and Activator Protein (AP)-1 (8,9). Interaction of the Amadori-glucose epitope with specific cell-associated binding proteins is believed to trigger these and likely other effects (9–12). Amadori-modified albumin also increases Plasminogen Activator Inhibitor-1 (PAI-1) expression, induces NF- κ B and AP-1 DNA binding activity and upregulates Vascular Endothelial Growth Factor (VEGF) expression in peritoneal mesothelial cells (13,14), findings believed to be contributory to neoangiogenesis and structural alterations in the peritoneal membrane in patients undergoing peritoneal dialysis that also may be relevant to cellular activation and plaque formation in atherosclerosis.

Aortic endothelial cells express receptors specific for Amadori-modified albumin (15,16) and exhibit reduced replicative capacity and production of basement membrane type IV collagen when cultured in the presence of Amadori-modified albumin, consistent with a receptor-mediated maladaptive response (17). Endothelioma and umbilical vein endothelial cells respond to exposure to this glycated protein with enhanced nitric oxide synthase (NOS) activity and expression, increased nitric oxide (NO) production, and elevated NO-dependent apoptosis (18,19). A glycated albumin-induced imbalance in eicosanoid production, particularly affecting thromboxane (18), may help explain the seeming paradox of elevated NO in the context of proatherogenic endothelial dysfunction. Additionally, glycated albumin stimulates adhesion of monocytes to endothelial cells through enhanced transcription of the cell surface adhesion molecules E-selectin, vascular cell adhesion molecule-1 and intercellular adhesion molecule-1 (20), implicating it in the initial endothelial cell activation occurring at atherosclerosis-prone vascular sites (21,22).

In vascular smooth muscle cells, Amadori-modified albumin induces several relevant chemokine and mitogen responses, including increased expression of the inflammatory factors Monocyte Chemoattractant Protein (MCP)-1 and Interleukin (IL)-6. These changes are ascribed to a glycated albumin-stimulated production of reactive oxygen species and of inducible (i) NOS, and activation of NF- κ B, AP-1, mitogen activated protein kinase (MAPK) kinase, and tyrosine kinase (23–25). Increased MCP-1 and IL-8 in response to glycated albumin also has been observed in corneal keratocytes, attesting to the notion that the glycated protein can function as a circulating chemokine inducer (26). Glycated albumin stimulates mitogenesis in vascular smooth muscle cells via the MAPK pathway through activation of ERK by Protein Kinase C (PKC) isoforms (27).

Thus, *in vitro* studies indicate that physiologically relevant concentrations of Amadori-modified albumin possesses multiple proatherogenic effects that include promoting oxidative stress, production of inflammatory mediators, endothelial damage, and vessel wall hypertrophy. The hypothesis that glycated albumin augments oxidative stress and free radical impairment that contribute to atherogenesis in diabetes is supported by the finding that conformational shifts in the albumin molecule attendant to the formation of Amadori adducts, without the extensive damage to the folded structure that is typically induced by AGE, can affect anti-oxidant properties of the protein and foster acquisition of pro-oxidant activity in the presence of copper (28–30).

Although direct corroboration that pathobiologic effects of glycated albumin that have been demonstrated *in vitro* have relevance to the *in vivo* development of atherosclerosis in diabetes is lacking, such evidence exists with respect to the pathogenesis of diabetic nephropathy, which falls under the broad rubric of vascular complications of diabetes. Data from experiments with glomerular mesangial and endothelial cells have established that an increased level of Amadori-modified albumin is sufficient stimulus to set into motion a pathogenic program characterized

by alterations in key cellular mediators that modulate cell signaling pathways which are important in regulating extracellular matrix production (ECM) and are known to participate in the development of diabetic nephropathy. Specifically, human albumin containing Amadori-glucose adducts has been shown to stimulate the expression of $\alpha 1$ (IV) collagen and fibronectin, prominent constituents of the expanded ECM that is seen in diabetic glomeruli (31–36), activate PKC- $\beta 1$ and ERK (37–39), and increase expression of mRNA encoding the fibrogenic TGF- $\beta 1$ and its primary signaling receptor, the TGF- β type II receptor (35,39,40). Glycated bovine albumin increases human mesangial cell PKC- α activity and superoxide production, and induces transcription of PAI-1 through Smad-3 DNA-binding in the PAI-1 promoter (41,42). The hypothesis formulated from *in vitro* findings that Amadori-modified albumin is an independent and potent trigger of molecular mediators contributory to complications of diabetes is documented by results of experimental animal studies showing that neutralizing the biologic effects or inhibiting the formation of glycated albumin can ameliorate structural, functional and cell biology abnormalities in the kidney and retinal microvasculature of diabetic rodents, and can do so in the face of persistent hyperglycemia (43–48). Support for this hypothesis in the clinical arena can be found in studies showing that the concentration of Amadori-modified albumin is independently associated with diabetic nephropathy and retinopathy (49–51), and that the localization of glycated albumin in patients with diabetic nephropathy corresponds with severity of renal involvement (52).

In the context of the above discussion as well as that which follows, it is worth noting the view that analogous pathogenic mechanisms may contribute to atherosclerosis and progressive renal disease (53). Endothelial dysfunction is closely associated with both micro- and macrovascular disease in diabetes (54), and there are biochemical and histological similarities between systemic atherosclerosis and glomerulosclerosis (55,56), including a noxious role for oxidized LDL, intrinsic alterations in extracellular matrix, growth factor and cytokine-stimulated proliferation and collagen production, and eventual sclerosis (57).

Lipoproteins

Low Density Lipoproteins

Nonenzymatic glycation of Apolipoprotein B (Apo B) in low density lipoproteins (LDL) is considered to be a proatherogenic modification contributory to the increased susceptibility of patients with diabetes to atherosclerotic disease. Early work showed that the internalization and degradation by cultured fibroblasts of LDL from patients with poorly controlled diabetes and elevated levels of glycated LDL were decreased compared with that observed with LDL isolated from nondiabetic subjects or from patients with diabetes having good metabolic control (58). Other contemporaneous and subsequent studies demonstrated that glycation diminishes the uptake and degradation of LDL by the high affinity LDL receptor, promotes uptake and metabolism by alternative pathways (59–62), decreases the rate of clearance of LDL *in vivo* (63), compromises regulation of hydroxymethylglutaryl-CoA reductase and acyl-CoA:cholesterol transferase activities (64,65), and accelerates free radical production and increases lipid peroxidation (66–69), which can enhance LDL atherogenicity through recognition and internalization of oxidized Apo B adducts by macrophage scavenger receptors and formation of foam cells (70,71). Macrophage uptake of glycated LDL is greater than that of control LDL (72).

Glycated LDL has been shown to induce functional changes in various cell types including enhancement of chemotactic properties in monocytes (73,74), stimulating migration and proliferation of smooth muscle cells (75,76), and increasing platelet aggregation, nitric oxide production, and Ca^{+2} -ATPase activity (74,77). Activation of the MAPK pathway with increased ERK phosphorylation and PKC activity and of STAT5 with increased src kinase activity and p21^{waf} expression have been invoked in the mediation of glycated LDL effects in

smooth muscle and endothelial cells (78,79). Additionally, glycation of LDL increases its interaction with arterial proteoglycans, a property considered to have atherogenic importance (80). This effect has to be reconciled with the observation that lipoprotein lipase-enhanced binding, uptake and degradation of glycated LDL by fibroblasts, endothelial cells and peritoneal macrophages, which operate via mechanisms independent of the LDL-receptor (LDL-R) and the LDL-R-related protein, appears to require association of the enzyme with cell surface glycosaminoglycans (81).

In addition to direct proatherogenic biologic effects, the capacity of glycated LDL for vascular damage is accentuated by its propensity to promote oxidation of the apolipoproteins themselves and the lipids in the particle core, yielding glycoxidized LDL. Further, formation of glycated ethanolamine phospholipids in the LDL complex augments susceptibility of lipid moieties to oxidation (82). In many but not all studies, glycoxidized LDL has been found to exaggerate cellular responses such as those cited above (73,76,78,79). Glycoxidized LDL-induced mRNA expression of MCP-1 in endothelial cells is mediated through activation of NF- κ B in a process that availability of vascular NO may help prevent (83).

Increased glycation of the lipid transport apolipoprotein E is found in diabetic patients (84). Glycation of Apo E does not affect its binding to the LDL receptor in fibroblasts or the scavenger receptor A in macrophages, but has been shown to decrease binding to heparin and heparan sulfate, a functional alteration considered to affect sequestration and uptake of Apo E-containing lipoproteins by cells (84,85). Thus, glycation of apo E-containing lipoproteins has been suggested as contributory to atherogenicity by disturbing their heparan sulfate proteoglycan-mediated uptake.

Evidence for the participation *in vivo* of glycated LDL in atherogenesis can be found in results from animal experiments and from studies of human atherosclerotic plaques. Syrian hamsters made diabetic with streptozotocin, which develop atheromatous lesions in the aortic arch, exhibit an elevated concentration of glycated LDL that is more susceptible to oxidation, and glycoxidative products are immunochemically detectable in the foam cells of fatty streaks (86). Glycated ethanolamine lipids have been identified in atherosclerotic plaques collected from diabetic and nondiabetic subjects (82). Nonobese diabetic mice, although resistant to high fat diet-induced atherosclerosis, display an increased cellular immune response to glycated LDL and an increased LDL susceptibility to oxidation (87). In patients with type 2 diabetes and macrovascular disease, serum levels of antibodies to glycated LDL were not significantly different from those in nondiabetic patients with coronary artery disease or healthy controls, but the LDL from diabetic subjects showed greater susceptibility to oxidation (88). An immunologic study using epitope specific antibodies detected LDL glycoxidation products in macrophage-derived foam cells in fatty streaks, and nonoxidized glucose-modified products in the extracellular matrix (89).

Plasma concentrations of glycated LDL, measured by several different methods, are increased in diabetic patients (90–93) and show positive associations with other markers of cardiovascular disease such as serum cholesterol and triglyceride levels (94). Interestingly, the amount of Amadori-modified LDL correlates positively with microalbuminuria (94), a marker of inflammation and an independent risk factor for cardiovascular mortality (95) that has been found to be associated with increased cardiovascular mortality in type 1 and type 2 diabetes (96–99) as well as in subjects without diabetes (100), and is considered a predictor of mortality in non-insulin dependent diabetes (101,102).

High Density Lipoproteins

Glycation of Apo-AI, the major protein of the protective high density lipoprotein (HDL) complex is increased in diabetic patients (103) and has been shown to induce conformational

changes and decreased stability of the lipid-protein interaction and of the ability of the lipoprotein to self-associate (104–106). Some studies have shown increased lipid peroxidation and decreased activity of the HDL-associated anti-atherogenic paraoxonase enzyme in HDL subjected to short term glycation *in vitro* (106,107) but others have found that HDL susceptibility to oxidation is not affected by *in vitro* glycation (108). HDL glycated *in vitro* and Apo AI isolated from diabetic subjects exhibit diminished ability to activate lecithin:cholesterol acyltransferase, which drives reverse cholesterol transport by esterifying the cellular cholesterol removed by HDL (109,110). HDL glycated *in vitro* did not show diminished capacity to mediate cholesterol efflux (108), but transfer rates of cholesteryl ester from HDL to apo-B containing lipoproteins have been reported to be greater in glycated lipoproteins prepared from diabetic compared to nondiabetic subjects (111). However, subjecting the cholesteryl ester transfer protein to *in vitro* glycation has been found to impair its activity (111). Other potential functional effects ensuing from nonenzymatic glycation of HDL have been examined in human aortic endothelial cells. Glycated and glycoxidized HDL induce H₂O₂ formation, dampen expression of endothelial NOS and decrease NO production (112), promote apoptosis that is associated with increased caspase 3 expression and is attenuated by caspase 3 inhibition, and increase release of cytochrome c into the cytosol (113). These structure/function alterations consequent to nonenzymatic glycation of Apo AI/HDL are consistent with a proatherogenic role in the accelerated atherosclerosis in diabetes.

Therapeutic Implications

The experimental evidence linking Amadori-modified serum proteins to accelerated atherogenesis in diabetes suggests that preventing the nonenzymatic glycation of relevant proteins or blocking their biological effects might beneficially influence the evolution of atherosclerosis in diabetic patients. Considering that glycation renders LDL more susceptible to oxidation, and the established causal role of oxidized LDL in atherogenesis, it is presupposed that inhibiting the formation of glycated LDL in diabetic patients could reduce the propensity for LDL oxidation and atherosclerotic disease. Some old and some new agents may hold promise in this regard, either directly or as models for development of new therapies. The anti-platelet agent diltiazem and a fenofibrate metabolite, fenofibric acid, have been found to prevent MCP-1 expression stimulated by glycoxidized LDL in human endothelial cells (114). Peroxisome proliferator-activated receptor (PPAR) activators reduce uptake of glycated LDL in human monocyte-macrophages by reducing lipoprotein lipase-stimulated binding and uptake (81,115). Administration of a monoclonal antibody directed against Amadori-glucose epitopes in glycated albumin or a small molecule that inhibits the condensation of glucose with albumin has been shown to ameliorate nephropathy in diabetic rodents (43,44,47,48), but potential anti-atherogenic effects of these agents have not been investigated.

The endogenous dipeptide carnosine (beta-alanine, histidine) possesses anti-glycation activity as well as free radical and metal ion-scavenging properties, due in part to its nonenzymatic reaction with carbonyl groups on glycoxidized proteins and its ability to stabilize adducts formed at the primary amino group through the imidazolium group of the histidine residue (116–119). These observations have advanced the hypothesis that carnosine is a protective factor with properties that may reduce the glycation of proteins and its consequences. In an *in vitro* model of lens α -crystallin glycation, believed to be involved in cataractogenesis, carnosine decreased glycation-induced tryptophan fluorescence and disaggregated glycated α -crystallin (120). Administration of carnosine prevented a “diabetes-associated” rise in blood pressure in fructose-fed rats and elevated levels of TNF- α and IL-6 in diabetic mice (117, 118,120,121). Recently, Janssen *et al* reported that susceptibility for diabetic nephropathy associates with a trinucleotide repeat in the leader peptide of the CNDP1 gene (122), located in chromosome 18q22.3, a locus that has been previously linked to diabetic nephropathy (123–125). This gene encodes for the carnosine-degrading enzyme carnosinase and, coupled

with the finding that patients with a higher number of CNDP1 leucine repeats in the leader peptide had higher serum carnosinase levels, suggests that susceptibility for nephropathy relates to reduction of carnosine and the anti-glycation protective effects it may afford. The involvement of CNDP1 in diabetes-related atherosclerosis remains to be determined.

A report that long-term dietary supplementation with the amino acid taurine increases survival in streptozotocin-diabetic rats (126) might be provocatively related to the observations that taurine and its precursor hypotaurine can competitively inhibit protein glycation by forming Schiff bases with sugar carbonyls (127) and that taurine can lower levels of glycated proteins in fructose-fed rats (128). Other studies have reported that taurine prevents glucose-induced decrease in erythrocyte Na^+/K^+ and Ca^{2+} -ATPase activities (129), lowers cholesterol in genetic GK and streptozotocin-induced diabetic rats fed a high cholesterol diet (130,131), and reduces lipid peroxidation and plasma levels of triglycerides and LDL-cholesterol in streptozotocin-diabetic rats (132).

Several plant substances are of interest for their anti-glycation, and in some instances anti-glycoxidation, activities. A derivative of the bioflavonoid rutin significantly reduced the formation of Amadori-modified proteins in tissues incubated in the presence of high glucose (133). Garcinol, a benzophenone derivative in fruit rind, and extracts from several other plant tissues show glycation-inhibitory properties in a bovine serum albumin/fructose model system (134,135). Penicillamine also inhibits the formation of Amadori adducts when human serum albumin is incubated in the presence of 20 mM glucose (136). The soy flavonoid genistein prevents LDL peroxidation mediated by glycated LDL, although it does not affect the formation of glycated LDL (137).

Conclusions and Perspectives

In the diabetic state, the accelerated formation of Amadori-modified glycated serum proteins and lipoproteins fosters the pathogenesis of atherosclerosis. This complex process, involving upregulation of inflammatory signaling pathways, elaboration of chemokines and cytokines, adherence of monocytes/macrophages and platelets, endothelial dysfunction, smooth muscle proliferation and migration, increased uptake of LDL, reduced effectiveness of HDL, cellular apoptosis, and oxidative injury, is abetted by glycated proteins at almost every step. Preventing the formation of Amadori-modified proteins, particularly the abundant circulating species albumin and LDL, should hinder many of the pathophysiologic processes that culminate in atherosclerosis, and the efficacy of anti-glycation agents in this regard has been suggested by clinical evidence from studies of diabetic nephropathy. However, more pointed investigations to test the anti-atherogenic capacity of Amadori inhibition seem promising and should be forthcoming. If euglycemia cannot be achieved, which unfortunately is the case in large numbers of patients with diabetes, complementary therapy to limit the nonenzymatic condensation of glucose onto proteins or lipoproteins may attenuate the atherosclerotic process. Other opportunities for intervention could include reducing the burden of Amadori-modified serum proteins by “deglycation”, assuming conversion to irreversible AGE has not occurred, or interrupting receptor-mediated cellular activation, once the appropriate receptors and signaling pathways are clearly defined. Forestalling atherosclerosis, especially in diabetes, will greatly diminish the scourge of heart disease and stroke, the number-one and number-three leading causes of death in the industrialized nations of the world.

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