Interventional
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The association of coronary artery disease and advanced glycation end-products

Abstract

Traditional risk factors are insufficient to explain all cases of Coronary Artery Disease (CAD) in patients with Diabetes Mellitus (DM). Hyperglycemia is the hallmark feature of DM. An increase in the incidence of both micro-and macrovascular complications of diabetes has been observed with increased duration of hyperglycemia. This association persists even after glycemic control has been achieved, suggesting an innate mechanism of "metabolic memory." Advanced Glycation End products (AGEs) are glycated proteins or lipoproteins that may serve as mediators of metabolic memory due to their increased production in the setting of hyperglycemia and generally slow turnover. Elevated AGE levels can lead to abnormal cross linking of extracellular and intracellular proteins disrupting their normal structure and function. Furthermore, activation of AGE receptors can induce complex signaling pathways leading to increased inflammation, oxidative stress, enhanced calcium deposition, and increased vascular smooth muscle apoptosis, contributing to the development of atherosclerosis. Through these mechanisms, AGEs and their receptors may play important roles in the development and progression of CAD. However, clinical studies regarding the role of AGEs and their receptors in advancing CAD are limited, with contradictory results. Further studies are needed to evaluate the utility of circulating and tissue AGE levels in identifying asymptomatic patients at risk for CAD or to identify patients who may benefit from invasive intervention.

Keywords: Advanced glycation end products • Atherosclerosis • Coronary artery disease • Glycated proteins • Hemoglobin A1c

Craig Basman[1*], Sarah L Fishman[2], Varinder Singh[1], Leonid Poretsky[2]

[1]Department of Cardiovascular Medicine, Lenox Hill Hospital, Northwell Health, New York, NY, USA

[2]Division of Endocrinology and Friedman Diabetes Institute, Lenox Hill Hospital, Northwell Health, New York, NY, USA

*Author for correspondence:
Craig Basman, Department of Cardiovascular Medicine, Lenox Hill Hospital, Northwell Health, New York, NY, USA, E-mail: cbasman@northwell.edu

Abbreviations

CAD: Coronary Artery Disease; DM: Diabetes Mellitus; AGEs: Advanced Glycation End products; HbA1c: Hemoglobin A1c; CML: Nϵ-(Carboxymethyl) Lysine; sRAGE: soluble AGE Receptor.

Introduction

While the risk of Coronary Artery Disease (CAD) is higher in patients with Diabetes Mellitus (DM), the causal link has not yet been established. Hyperglycemia alone may not account for this risk as some landmark diabetes trials have shown that intensive glycemic control does not reduce cardiovascular events compared to standard therapy[1-3] Other studies [4,5], however, indicated that long term improved glycemic control reduces the risk of acute coronary events. Advanced Glycation End-products (AGEs), a heterogeneous class of glycated proteins and lipoproteins, have been associated with the development of atherosclerosis [6-10]. AGEs have been linked to a variety of pathological states, including chronic kidney disease and Alzheimer's disease.

In individuals with diabetes, AGEs have been independently associated with cardiovascular morbidity and mortality [11,12]. The purpose of this review article is to analyze the relationship of AGEs and CAD.

What are AGEs and their receptors?

AGEs are a heterogeneous class of glycated proteins and lipoproteins. AGE accumulation can occur through endogenous synthesis or exogenous delivery through dietary intake. Though there are many AGEs, the most studied are hemoglobin A1c (HbA1c), glycated albumin, pentosidine, N∈-(carboxymethyl)lysine (CML) and their soluble receptor, sRAGE. AGEs can accumulate in nearly every tissue including brain, heart, eye, and kidney, binding to many extracellular and intracellular proteins in a variety of cell types. Activation of receptor for AGE (RAGE) by AGE binding initiates complex signaling pathways. Both AGEs and RAGE levels have been associated with atherosclerosis in patients with and without DM [13-15].

Association of AGEs and CAD

Evidence suggests that serum and tissue AGE levels may predict both the presence and the burden of CAD. Kerkeni, et al. found that pentosidine, not CML, was higher in patients with CAD irrespective of diabetic status (diabetic population; p=0.032 and non-diabetic population; p=0.002) [16]. In a cross-sectional analysis, Lu, et al. found that elevated glycated albumin and reduced sRAGE levels correlated with the severity of CAD and progression of atherosclerosis in patients with DM [17]. Kiuchi, et al. found that circulating AGE levels were higher in diabetic patients with obstructive CAD than non-obstructive CAD [18]. However, our group has previously published conflicting results, whereby AGE and sRAGE levels did not significantly correlate with the presence or degree of obstructive CAD [19]. Table 1 summarizes the studies analyzing the relationships between AGE levels and CAD.

Table 1: Studies investigating the relationship between AGEs and CAD.			
Reference	**Type**	**(n)**	**Result**
Nin, et al. [12]	Observational Patients with type 1 DM were observed for incidence of cardiovascular events	339	The incidence of cardiovascular events correlated with baseline circulating AGE levels over a median follow-up period of 12 years. However, this association did not remain significant when patients with baseline nephropathy were excluded
Kiuchi, et al. [18]	Observational study of patients undergoing coronary angiography for suspected CAD or with chest pain	83	AGE concentrations were significantly higher in patients with CAD who had DM compared to those without DM (2.8 vs. 5.5 mU/mL, respectively (p<0.0125). However, AGE concentrations did not show a significant difference in patients without CAD between patients with and without DM. There was a significant association between AGE levels and severity of CAD in patients with DM (single vessel: 3.4 mU/mL, two vessels: 5.7 mU/mL, and three vessels: 7.2 mU/mL). There was no significant correlation between AGE levels and severity of CAD in patients with or without DM.
Lu, et al. [17]	Cross Sectional study of patients undergoing coronary angiography	1320	Elevated glycated albumin and reduced esRAGE levels correlated with the severity of CAD and progression of the plaque in patients with DM (p<0.01). There were no significant differences in glycated albumin and esRAGE concentrations (in patients without DM) between patients with and without CAD.
Kanauchi, et al. [40]	Observational study of patients undergoing coronary angiography for suspected CAD or with chest pain	98	There were significantly higher AGE levels in patients with CAD and DM compared to control individuals (2.42 ± 0.65 vs. 1.96 ± 0.40 mU/mL, p<0.01). The AGE concentrations significantly correlated with the severity of CAD (no CAD: 1.98 ± 0.29; 1 vessel: 2.09 ± 0.34; 2 vessels: 2.60 ± 0.73; and 3 vessels: 3.18 ± 0.58 mU/ml, p<0.0001).
Kerkeni, et al. [16]	Cross sectional study of patients undergoing coronary angiography for suspected CAD or chest pain	161	Serum pentosidine concentrations were significantly higher in patients with CAD in both patients with and without DM (p=0.032 and 0.002, respectively). CML levels did not show a significant difference in patients with CAD between those with and without DM. The serum pentosidine concentrations were significantly higher in patients with CAD who had a Gensini score of > 20 compared to those with the score of "1-20" or "0" (p=0.002 and p<0.001, respectively). CML concentration was not associated with the severity of CAD (p=0.853).
Basta, et al. [41]	Cross sectional study of patients who underwent successful percutaneous coronary intervention.	81	AGE concentrations were significantly higher in patients with multi-vessel CAD compared to those with single vessel disease at both day 1 and day 180 after PCI (p=. 0.033 and 0.005, respectively), but not before PCI (p=. 0.60). There was a significant increase in sRAGE levels at 180 days (491 µg/ml [374-850]) compared to before and 1 day after PCI (406 µg/ml [266-575] and 393 µg/ ml [222-554] respectively, p= 0.011). There was a correlation between CML levels and the extent of the stenting on day 1 and day 180 (p=0.022 and p=0.012, respectively).
Basman, et al. [19]	Cross sectional study of patients undergoing elective cardiac catheterization.	364	AGE and sRAGE levels did not significantly correlate with any of the studied coronary artery disease parameters. HbA1c showed positive correlation with both SYNTAX and SYNTAX II scores in patients with and without diabetes.

Association of HbA1c and CAD

HbA1c has been identified as an independent predictor of CAD burden. Even, in patients without diabetes, a high-normal HbA1c level has been linked with an increased risk of CAD [6,20,21]. Additionally, HbA1c is also an independent risk factor for mortality in non-diabetic patients [22]. Previous results published by our group also found that elevated HbA1c levels correlate with the burden of CAD in both diabetic and non-diabetic patients [19]. This association is important not only because it may help identify patients at risk for cardiovascular events, but also because in patients presenting with acute coronary syndrome, a higher HbA1c may be associated with worse outcomes [23]. In one study, for every 1% increase in HbA1c level there was a 24% increase in mortality among non-diabetic patients presenting with ST elevation myocardial infarction. Interestingly, HbA1c level did not impact mortality among diabetic patients in this study [24], but in the larger Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction trial, HbA1c was an independent predictor of mortality among individuals with diabetes [25]. Table 2 lists a summary of trials investigating the link between HbA1c and outcomes among patients with ACS.

Table 2: Studies investigating the relationship between HbA1c and CAD.			
Reference	**Type**	**(n)**	**Result**
Cicek, et al. [23]	Prospective study in patients hospitalized with STEMI	374 (diabetic and non-diabetic)	HbA1c an independent predictor of mortality in patients presenting with STEMI
Gustafsson, et al. [24]	Retrospective data from the MI and heart failure from the OPTIMAAL trial	2841 (diabetic and non-diabetic)	Increasing HbA1c levels associated with higher mortality rate among patients without diabetes history. HbA1c had no impact on mortality among the patients with known diabetes
Malmberg, et al. [25]	Retrospective data from the Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction trial	620 (diabetic)	HbA1c was an independent predictor of mortality in diabetic patient
Chowdhury, et al. [29]	Retrospective, multi-center study	301 (non-diabetic)	Elevated HbA1c was associated with short-term mortality after STEMI in nondiabetic patients

As data accumulates, the association between HbA1c and cardiovascular events/outcomes is becoming clearer [26]. Yet, it remains unclear why this relationship exists. One hypothesis suggests that as a long half-life protein, HbA1c may be involved in a chronic inflammatory response resulting in accelerated atherosclerosis.

Mechanism of Cardiovascular Disease Induced by AGE/RAGE Pathway

The pathogenic effects of AGE occur *via* several mechanisms including:

1) Modification of extracellular proteins

2) Modification of intracellular proteins

3) The binding to cell surface RAGE and activation of signaling cascades

Modification of extracellular proteins

AGEs can modify the structure of extracellular proteins such as collagen, elastin and laminin. This alters the protein function and may induce an inflammatory response. After these proteins become glycosylated, they may crosslink with other extracellular proteins and become resistant to proteolytic digestion [27], and increase vascular stiffness (or in the myocardium would result in impaired relaxation) [28]. Similarly, glycation of LDL molecules alters their shape which inhibits their re-uptake by LDL receptors. After LDL is unable to be cleared from the circulation it becomes oxidized and triggers the formation of foam cells (resulting in atherosclerosis) [29].

Modification of intracellular proteins

The accumulation of AGES in the endoplasmic reticulum causes impairment of normal protein folding. Intracellular AGEs bind to mitochondrial proteins that are involved in the electron transport system. This results in a decrease in adenosine triphosphate synthesis and production of reactive oxygen species [30]. In the myocardium, these intracellular AGEs alter calcium homeostasis and result systolic dysfunction [31].

Activation of signaling cascade

The AGE/RAGE axis activation generates a signaling cascade that results in the initiation of an inflammatory response [7]. The activation of RAGE results in translocation of NFκβ to the cell nucleus whereby it enhances expression of inflammatory cytokines (including IL-6, TNFα, TGF-β, and vascular adhesion molecules). These cytokines result in vascular inflammation (through stimulation of fibrotic, proliferative and thrombogenic pathways) [7]. The AGE/RAGE axis also produces reactive oxygen species through NFκβ mediated upregulation. AGEs can also directly inactivate nitric oxide (which has a wide range of vascular

properties including regulation of local cell growth, modulation of vascular tone and protection of blood vessels from reactive oxygen species) [7].

Potential Therapies

There has been multiple studies (both *in vitro* and animal) showing that reducing AGE levels may lead to a reduction in micro and macro-vascular DM complications. Reduction of these levels has been achieved through several mechanisms. There are compounds that inhibit AGE formation through anti-oxidant properties. The use of compounds such as aminoguanidine in rodents has resulted in a reduction in atherosclerotic plaque and improvement in myocardial function [32]. However, safety concerns such as nephrotoxicity exist for these compounds in humans [33]. Another way to reduce AGE formation is with sRAGE infusions. Infusion of sRAGE (or RAGE inhibitors) has been shown to reduce atherosclerotic burden in rodents, however to our knowledge these have not been tried in humans yet [34]. Lastly, reducing the dietary consumption of AGEs (or reducing intestinal absorption through the use of compounds such as sevelamer carbonate) has been shown to reduce HbA1c [7].

Discussion

There are several available therapies used for DM and cardiovascular disease that may reduce AGE levels by impacting the AGE/RAGE axis. Atorvastatin not only decreases LDL levels, but may increase esRAGE levels, thereby decreasing the accumulation of AGEs [35]. Rosiglitazone has also been shown to reduce esRAGE levels [36], and other oral hypoglycemics such as metformin and pioglitazone can block AGE formation [37]. Glucagon-like peptide-1 agonists may decrease RAGE expression, and linagliptin (a DPP4 inhibitor) suppresses activation of the AGE/RAGE axis [38]. Angiotensin converting enzyme inhibitors and angiotensin receptor blockers significantly attenuate AGE production [39-42].

Conclusion

Evidence supporting the role of AGEs in the progression of CAD in patients with and without DM continues to accumulate. While the literature has controversial results among various AGEs, the association of HbA1c and CAD development is strong. Additionally, an elevated HbA1c portends a poorer prognosis in patients that present with acute coronary events. Given the increasing evidence supporting a role for AGEs in promoting cardiovascular events, development of therapeutic agents aimed at reducing circulating AGE concentrations (or blocking of RAGE activation) may improve outcomes. Continued investigation and further studies are required.

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