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Glycosylated hemoglobin, but not advanced glycation end products, predicts severity of coronary artery disease in patients with or without diabetes

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ABSTRACT

Background: The association between coronary artery disease (CAD) and diabetes mellitus (DM) is strong but the physiologic mechanisms responsible for this association remain unclear. Patients with DM exhibit high circulating levels of glycated proteins and lipoproteins called advanced glycation end products (AGEs) which have been implicated in the development of oxidative damage to vascular endothelium. We examined the relationships between the presence and extent of CAD and AGEs in patients undergoing elective coronary artery catheterization in an urban teaching hospital.

Methods: Patients with possible CAD (n = 364) were recruited prior to elective cardiac catheterization (52% male, 48% diabetic). Regression and correlation analyses were used to examine the relationship between serum AGE concentrations, soluble AGE receptor (sRAGE) concentration, HbA_{1c}, LDL and the presence of obstructive CAD along with the burden of CAD measured by SYNTAX and SYNTAX II scores.

Results: AGE and sRAGE levels did not significantly correlate with any of the studied coronary artery disease parameters. HbA_{1c} showed positive correlation with both SYNTAX and SYNTAX II scores in patients with and without diabetes.

Conclusion: In this cross-sectional study of patients with possible CAD, serum AGEs and sRAGE concentrations did not correlate with SYNTAX or SYNTAX II scores regardless of diabetic status. HbA1C correlated positively with the SYNTAX and SYNTAX II scores in both diabetic and non-diabetic populations.

1. Introduction

While it is understood that diabetes mellitus (DM) increases the risk of coronary artery disease (CAD), it is unclear whether hyperglycemia leads to the excessive CAD risk in the diabetic population. Landmark diabetes trials such as the ACCORD, ADVANCE and Veterans' Affairs have shown that intensive glycemic control does not reduce cardiovascular events compared to standard therapy [1–3]. Yet other large trials have shown that patients with type 2 diabetes benefited from more intensive therapy, with a significant risk reduction for myocardial infarction and death [4]. Furthermore, in the diabetic population, hemoglobin A1c (HbA_{1c}) may be a predictor of CAD [5,6].

Advanced glycation end-products (AGEs) are a heterogeneous class of glycated proteins and lipoproteins. The accumulation of AGEs, such as methylglyoxal, glyoxal, carboxymethyl-lysine (CML), pentosidine, glucosepane, fructoselyine and their serum soluble receptor for AGE (sRAGE) has been implicated in a variety of

Abbreviations: AGEs, advanced glycation end products; CAD, coronary artery disease; CML- N(6), carboxymethyl-lysine; DM, diabetes mellitus; HbA_{1c}, hemoglobin A1c; LDL, low density lipoprotein; MACCE, Major adverse cardiovascular and/or cerebrovascular events; sRAGE, soluble AGE receptor.

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pathologies including CAD, chronic kidney disease and Alzheimer's disease. AGE levels have been correlated with increased arterial stiffness, vascular calcifications, and the development of atherosclerosis [7–10]. Furthermore, an elevated AGE level has been independently associated with cardiovascular morbidity and mortality in the diabetic population [11,12]. Several studies have found that circulating levels of a variety of AGEs (including glycated albumin, pentosidine, CML, and sRAGE) independently predict the presence and/or severity of CAD [13–16].

Though previous studies have demonstrated a correlation between AGE levels and CAD, the AGEs measured differed in each study and the overall numbers of subjects in each study were small. It therefore remains unclear if circulating levels of AGEs or their soluble receptor (sRAGE) can be used as a tool to risk stratify patients in the diabetic or non-diabetic populations for CAD. We sought to assess if serum levels of AGEs or their receptors may be useful for predicting the presence or severity of CAD in patients with and without diabetes mellitus suspected of having CAD. Furthermore, we analyzed the relationship between additional serum markers (including HbA_{1c} and LDL levels) and the presence of CAD in both diabetic and non-diabetic patients with possible CAD.

2. Materials and methods

Study Population: The study procedures received full approval from the Institutional Review Board at our institution. All subjects provided written informed consent to participate in this study. Enrollment procedures are summarized in Fig. 1. Three hundred sixty four patients ages 40–80 years old with no prior history of CAD who presented to our institution for diagnostic cardiac catheterization for suspected CAD were enrolled. All subjects underwent an invasive coronary angiogram and had serum levels of AGEs (Pentosidine, N(6)-carboxymethyl-lysine) and soluble receptor sRAGE analyzed by ELISA protein quantification.

Inclusion Criteria: Patients between the ages of 40–80 years old with no known history of obstructive coronary artery disease presenting for elective cardiac catheterization.

Exclusion Criteria: Active or recent infections (last one month), anti-inflammatory medications (NSAIDs) or corticosteroid treatment (in the last 4 weeks), cardiomyopathy/heart failure, hematological disorders (including severe anemia and hemolytic disorders), history of coronary artery bypass grafting, angioplasty or stenting, acute coronary syndrome, history of myocardial infarction, history of connective tissue disorders, history of previous major trauma or surgery (within 3 months), impaired renal function (creatinine >1.3 mg/dL), known cancer, liver dysfunction, or pregnancy.

Advanced glycation end-products: All patients were required to fast at least 8 h prior to obtaining blood samples for measurement of AGE levels. Serum AGE and sRAGE levels were measured by ELISA using commercially available kits following manufacturer's protocols. Information about the ELISA kits used and sensitivity of the assays is as follows: Human CML (G-Biosciences, Cat. # IT4530, sensitivity <9.4 ng/mL), Human Pentosidine (Biotang, Inc., Cat. # HU9354, sensitivity <15 pg/mL), Human RAGE (R&D Systems, Cat. # SRG00, sensitivity 1.23–16.14 pg/mL).

Coronary Angiography: Coronary angiography was performed through the radial artery or femoral artery by an experienced interventional cardiologist. Obstructive CAD was defined as a reduction of 50% or more in the luminal diameter of one or more major epicardial coronary artery branches. One interventional cardiologist blindly interpreted each angiogram. The severity of CAD was determined by the SYNTAX score [17]. Patients with nonobstructive or normal coronary arteries were given a score of 0. For all patients with obstructive CAD (SYNTAX score >0), the mortality risk associated with undergoing percutaneous coronary intervention or coronary artery bypass grafting was determined by calculating the SYNTAX Score II [18].

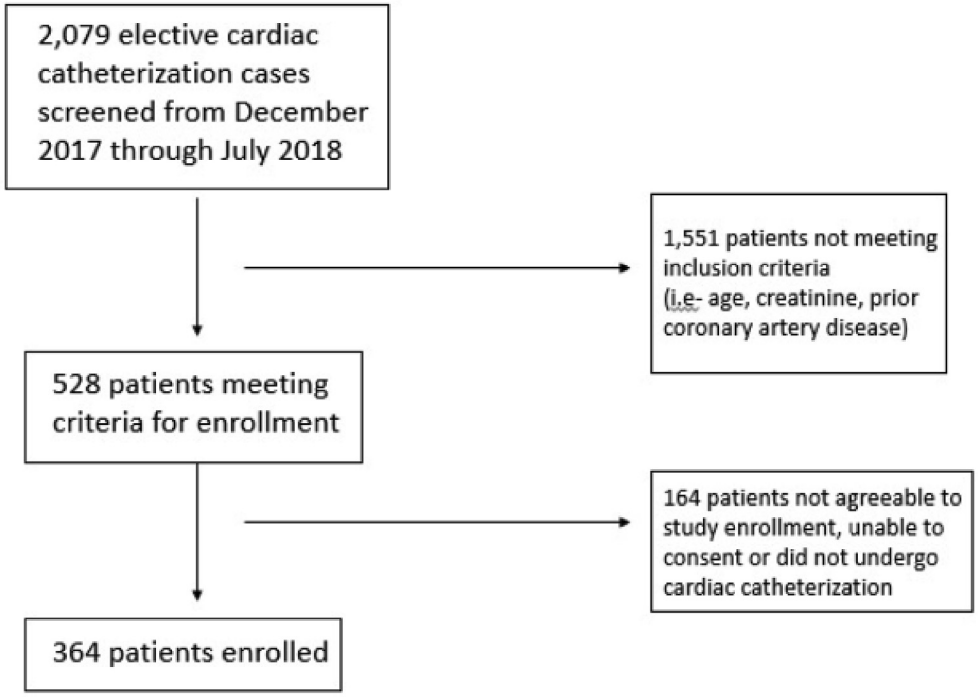

Fig. 1. Patient selection.

2.1. Statistical analyses

Descriptive statistics (n, mean, median, standard deviation, IQR, frequencies and percentages) were used to describe the demographic and clinical characteristics of the entire sample, as well as the DM and non-DM groups. Univariable logistic regression models were used to examine the association between obstructive CAD and pentosidine, CML, LDL, HbA_{1c}, sRAGE. The Spearman correlation coefficient was used to determine the strength of a monotonic relationship between each proposed factor and the SYNTAX score as well as SYNTAX Score II. Subgroup analyses were conducted for patients with and without diabetes. A result was considered statistically significant at the $p < 0.05$ level of significance. P-values and confidence intervals were not adjusted for multiple testing. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

3. Results

3.1. Baseline characteristics

The clinical characteristics of the patients enrolled in this study are displayed in Table 1. Male subjects comprised 52% of the study population. Diabetes was present in 48% of the subjects, and 22% were insulin-treated. The majority of patients had hyperlipidemia (80%) and were on statin therapy (72%). There were few active smokers (13%).

3.2. Correlations of serum AGEs, sRAGE and HbA_{1c} levels with CAD

Within the DM subgroup, 60% had obstructive CAD, while within the non-DM subgroup, 47% had obstructive CAD. Our study did not find any significant association between the presence of obstructive CAD (SYNTAX score > 0) and pentosidine ($p = 0.15$), CML ($p = 0.75$) or sRAGE ($p = 0.36$) levels (Supplementary Material 1). Furthermore, there was no statistically significant relationship between CAD burden (as measured by the SYNTAX score) or CAD mortality risk (as measured by SYNTAX Score II) and AGE levels (Fig. 2, Table 2). There was however, a statistically significant positive relationship between serum HbA_{1c} levels and presence of obstructive CAD ($p < 0.0001$) among all patients (Fig. 3, Table 2). Specifically, each unit increase in HbA_{1c} was associated with a 68% increase in the odds of having obstructive CAD (OR = 1.68, 95%CI: 1.36–2.09). A significant positive relationship was found in both the non-diabetic and diabetic patient subgroups (non-DM: OR = 1.88, 95%CI: 1.05–3.37, p = 0.03; DM: OR = 1.83, 95%CI: 1.33–2.52, p = 0.0002). This relationship was also found in subgroup analyses for non-diabetic and diabetic patients when spearman correlation was examined (non-DM: $\rho_S = 0.18$, $p = 0.01$; DM: $\rho_S = 0.29$, $p = 0.001$) (Fig. 4). There was also a positive relationship between HbA_{1c} and SYNTAX Score II ($\rho_S = 0.25$; $p < 0.0001$, and $\rho_S = 0.21$; $p < 0.0001$ for SYNTAX II PCI and SYNTAX II CABG respectively) (Table 3).

3.3. Correlation between serum AGEs, sRAGE, HbA_{1c} levels, and lipid profile

sRAGE levels were negatively correlated with those of pentosidine ($\rho_S = -0.14$, $p = 0.01$), positively with those of CML ($\rho_S = 0.14$, $p = 0.01$), and negatively with those of HbA_{1c} ($\rho_S = -0.11$, $p = 0.04$) (Supplementary Material 2). LDL levels did not correlate with pentosidine, CML, sRAGE, or HbA_{1c} (Table 4).

4. Discussion

We found that in 364 patients presenting for elective cardiac catheterization, AGE levels did not significantly correlate with the presence or burden of CAD. There was a positive correlation of HbA1c with the both the presence of CAD and the severity of CAD, as quantified by the SYNTAX score. In patients with obstructive CAD, HbA1c also correlated with SYNTAX Score II, a mortality prediction metric that incorporates anatomical and clinical characteristics to guide decision making between coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI).

Our results contrast with some previous studies which suggest that AGE levels are associated with CAD [13,14,16,19–24]. To our knowledge however, we present the largest cross-sectional study conducted thus far. There are significant differences in the study populations and methodology between previously published studies and the current study. Some previous studies reported differences in levels of AGEs in subjects with CAD in patients with DM, but not in those without DM [13,14,20], while other studies have suggested an association between AGEs and the risk of CAD in populations without DM [19,21]. It remains unclear to what extent increased HbA1C, above the level considered for a diagnosis of DM, impacts AGE levels. In our study, the population with DM had achieved excellent glycemic control, with an average HbA1C of 7.01%. Kiuchi et al. [13], presented data that demonstrated increased AGEs in patients with DM and CAD, however their study population had poor DM control with an average HbA1C of 8.5% and included a high percentage of smokers. Previously published

Table 1
Patient characteristics by DM status.

Variable	All patients N = 364 (%)	Non-DM patients N = 190 (%)	DM patients N = 174 (%)	P-value
Age, years (mean ± SD)	65.33 ± 10.51	64.56 ± 10.45	66.18 ± 10.57	0.1441
Body Mass Index (mean ± SD)	29.6 ± 6.7	29.4 ± 4.9	30.6 ± 6.8	0.2651
Gender, male	187 (51.52)	102 (53.68)	85 (49.13)	0.3862
Hyperlipidemia	290 (79.89)	134 (70.53)	156 (90.17)	<.0001
Hypertension	313 (86.23)	153 (80.53)	160 (92.49)	0.0010
Current smoker	49 (13.50)	19 (10.00)	30 (17.34)	0.0409
Use of Statin	262 (72.18)	117 (61.58)	145 (83.82)	<0.001
LDL (mean ± SD) (mg/dL)	86 (31)	90 (29)	82 (33)	0.01
HbA1c (mean ± SD) (%)	6.23 (1.29)	5.51 (0.54)	7.01 (1.41)	<0.0001
Pentosidine (mean ± SD) (pg/mL)	665 (522)	625 (524)	709 (515)	0.14
CML (mean ± SD) (ng/mL)	847 (110)	851 (113)	843 (105)	0.51
sRAGE (mean ± SD) (pg/mL)	1395 (897)	1407 (849)	1381 (945)	0.79
HDL (mean ± SD)	55.46 (17.31)	59 (18)	52 (16)	<0.0001

Data are expressed as mean ± standard deviation or number of patients (percentage). SD = standard deviation.

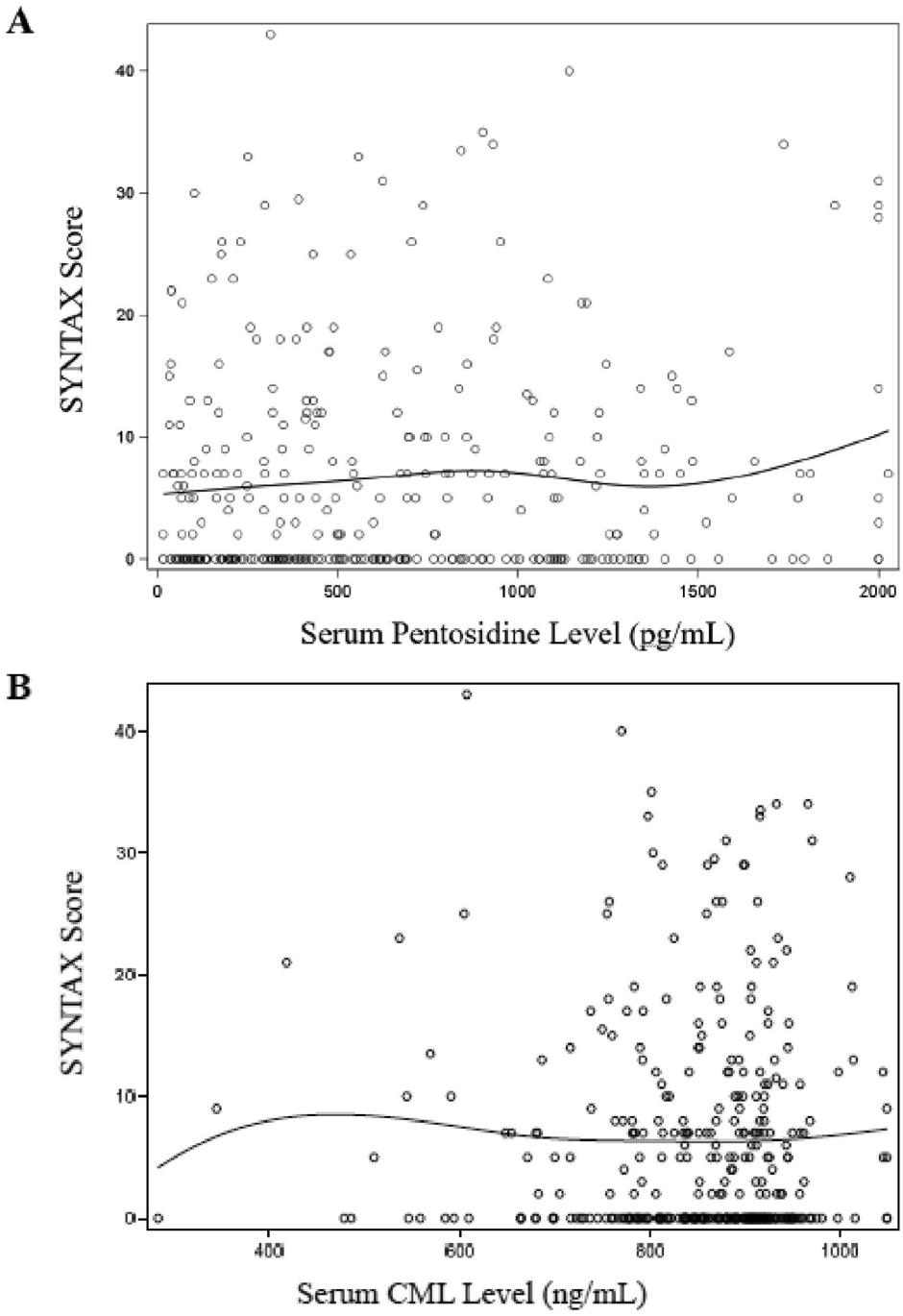

Fig. 2. Relationship of Advanced Glycation End-Products and Coronary Artery Disease. (A) No significant correlation of pentosidine levels and SYNTAX score. A penalized B-spline curve was used to fit the data points. (B) No significant correlation of CML levels and SYNTAX score. A penalized B-spline curve was used to fit the data points. (C) No significant correlation of sRAGE levels and SYNTAX score. A penalized B-spline curve was used to fit the data points.

studies identified an association between increased CML levels and CAD [21,22] however these studies examined populations with notable differences. For example, Semba et al. examined a population restricted to women over age 65, with significant disabilities and co-morbidities [22].

Differences in methodology may also account for the discrepant findings. Some previous studies did not specify the AGEs under investigation, reporting instead combined levels of a heterogeneous group of AGE molecules. Additional variability in the results may be attributed to differences in methods used to measure AGE levels. Multiple studies [16,24] reported that increased levels of pentosidine as measured by mass spectometry are associated with CAD, a finding our study failed to replicate when measuring pentosidine by ELISA. In addition to differences in population ethnicity, the current study evaluated the degree of coronary disease using SYNTAX score, in contrast to an older scoring system, the Gensini score, used by Kerkini et al. [16].

Elevated levels of serum sRAGE have been reported in patients

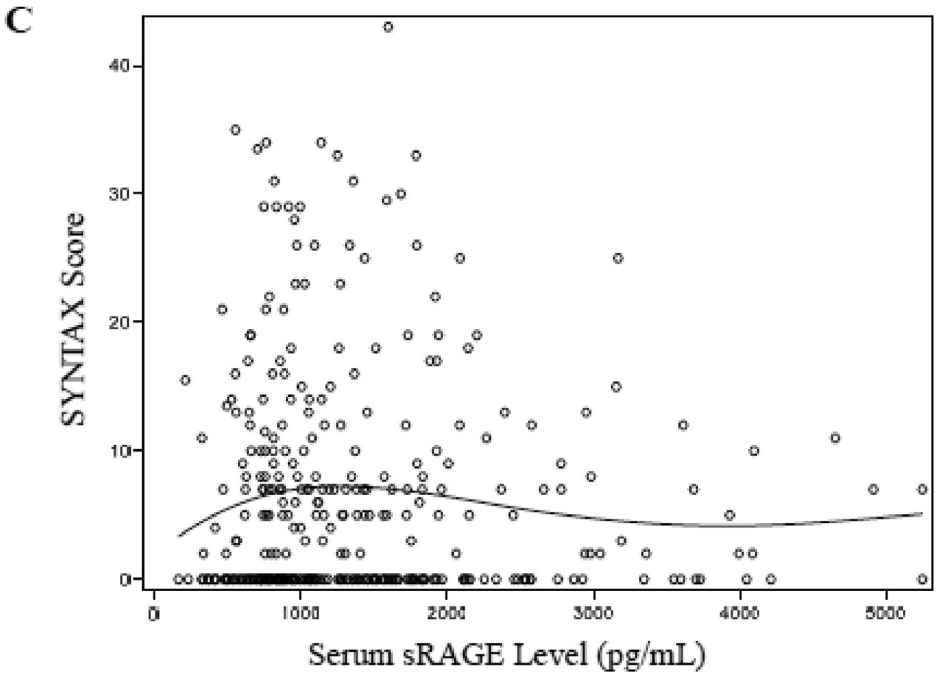

Fig. 2. (*continued*).

with diabetes and renal disease, while decreased levels have been associated with other chronic diseases including CAD, hypertension, heart failure, and hyperlipidemia. It has been hypothesized that the observed increase in sRAGE levels in patients with diabetes is a by-product of increased matrix metalloproteinase production (as a downstream effect of increased AGEs) leading to increased cleavage of sRAGE from the cell surface [20,25,26]. It may be difficult therefore to establish an association between sRAGE levels in patients with both DM and CAD.

We found that higher HbA_{1c} levels do not only predict the presence of CAD, but also the severity of CAD (as measured by the SYNTAX scores). HbA_{1c} is known to be an independent predictor for the severity of CAD. It has been suggested that high-normal glucose and HbA_{1c} level in patients without diabetes are associated with a higher risk of CAD [5,6]. Studies have also shown that in the patients with diabetes, HbA_{1c} is an independent risk factor for CAD [5,27]. There is also evidence that HbA_{1c} is a reliable tool for identifying patients at risk for cardiovascular events, including patients with no previous diabetes diagnosis [15]. Several studies have demonstrated that an elevated HbA_{1c} level is associated with poor outcomes in patients presenting with acute coronary syndrome [28,29].

Our study found that in patients with obstructive CAD, HbA_{1c} levels correlated positively with the SYNTAX Score II, a risk score for revascularization with both PCI and CABG. The SYNTAX Score II includes the SYNTAX score and seven other clinical variables (age, creatinine clearance, left ventricular ejection fraction (LVEF), presence of unprotected left main coronary artery disease, peripheral vascular disease, female sex, and chronic obstructive pulmonary disease) [18]. Though the presence of diabetes is not included in the SYNTAX Score II, HbA_{1c} levels correlated positively with both the SYNTAX II CABG score and SYNTAX II PCI score in our study.

Our data add to the hypothesis that HbA_{1c} is associated with atherosclerotic changes and imply that HbA_{1c} can be used to further risk stratify patients with possible CAD. However, it is not clear whether the relationship between HgA1c and CAD is entirely dependent on glycemic control. Genetic evidence supports a link between elevated HbA1c and a higher risk of CAD that is not only driven by glycemia, but also by glycemia-independent factors [30,31]. As a long half-life protein, HbA_{1c} may be involved in a chronic inflammatory response resulting in accelerated atherosclerosis.

Low-density lipoprotein (LDL) plays a significant role in the progression of atherosclerosis, and decades of research have demonstrated that lowering LDL reduces the risk of future cardiovascular events [32,33]. While the positive correlation between LDL levels and risk of major acute cardiovascular events has been demonstrated in several large meta-analyses, there is little evidence suggesting that higher LDL level predicts obstructive CAD [34,35]. In perhaps the largest meta-analysis, including almost 170,000 individuals, treatment with a statin was associated with a 22% proportional reduction in the risk of major cardiovascular events per millimole per litre reduction in LDL-C over a median of 5 years of treatment [36]. However, studies regarding LDL lowering medications in asymptomatic patients have not examined baseline angiograms to evaluate for the presence of obstructive CAD prior to study enrollment. Because there is a paucity of evidence that LDL is predictive of obstructive CAD, some investigators hypothesize that increased LDL is harmful because it is associated with a pro-inflammatory state, and not because it leads to a higher degree of obstructive CAD. Our study's subject number is too small to support this hypothesis and is also confounded by the proportion of patients on LDL lowering medications. In our study, LDL levels were significantly lower in patients with diabetes compared to patients without diabetes (mean LDL = 81.9 vs. 90.1, respectively; $p = 0.005$) probably reflecting a more aggressive treatment of hyperlipidemia in patients with diabetes. While LDL levels may help predict future cardiac events, they may not predict baseline obstructive CAD.

Our study shows that at the time of cardiac catheterization, the AGE levels which we examined do not predict the presence or burden of CAD. A study looking at different AGEs (including LDL-AGE and glycated albumin) might yield different results. In particular, recent studies have found that glycated albumin is superior to HbA_{1c} in assessing glycemic control [37]. It would therefore be interesting to see if future studies find glycated albumin levels to be predictive of CAD.

Table 2
Correlation of AGE levels and HbA1C with SYNTAX Score and SYNTAX II Score.

Variable	Spearman Correlation Coefficients		
	P-value		
	SYNTAX score	SYNTAX score II PCI	SYNTAX score II CABG
Pentosidine (n = 342)	0.08	0.05	0.05
	0.14	0.38	0.34
CML (n = 341)	0.00	0.06	0.07
	0.96	0.30	0.22
sRAGE (n = 338)	0.01	0.05	0.05
	0.80	0.41	0.34
HbA1C (n = 364)	0.26	0.28	0.21
	<0.001	<0.001	<0.001

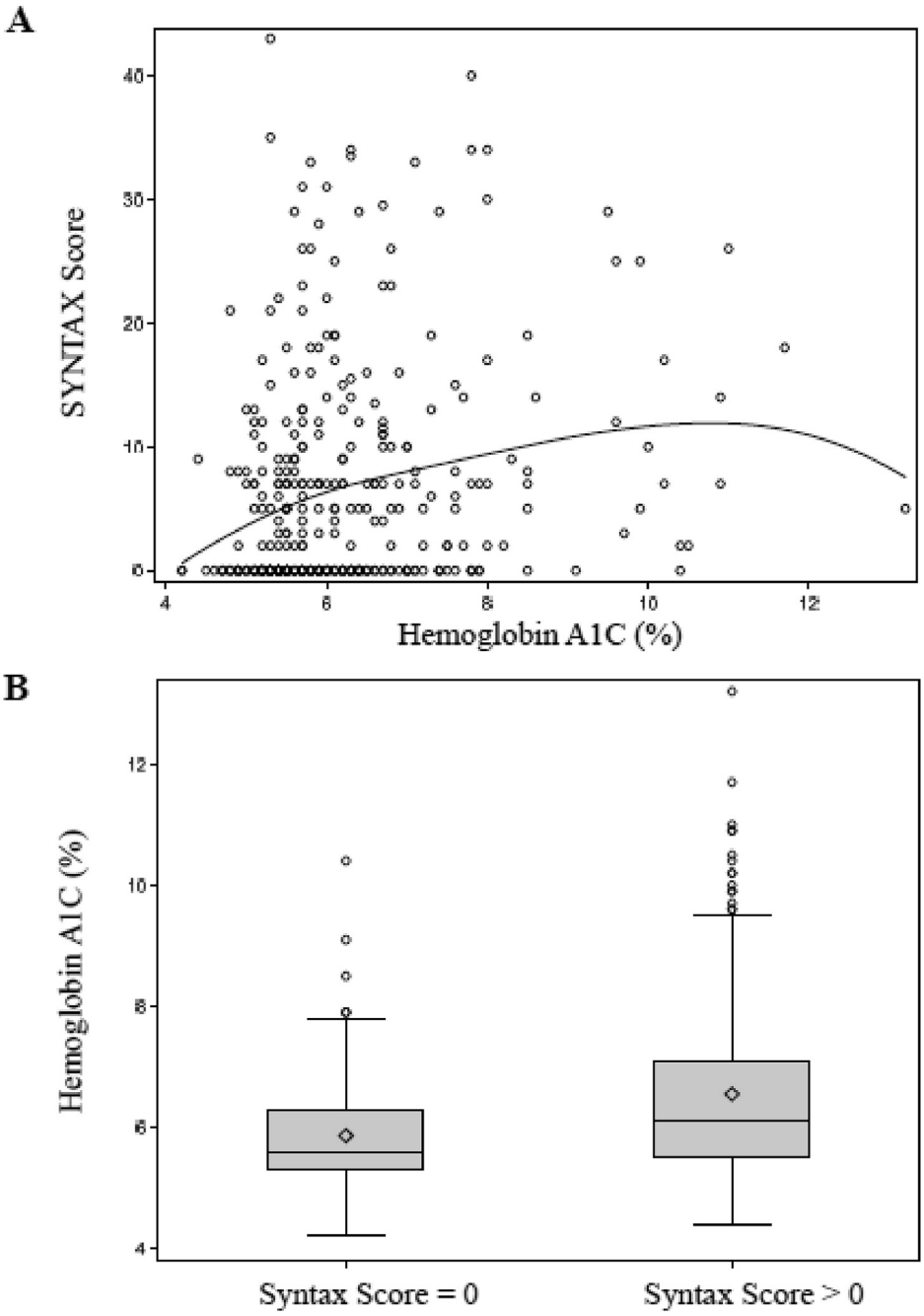

Fig. 3. Relationship of HbA1c and SYNTAX score. (A)- A positive correlation between HbA1c and the SYNTAX score ($p < 0.0001$, $r = 0.26$). A penalized B-spline curve was used to fit the data points.(B)- Patients with nonobstructive or normal coronary arteries have a lower HbA1c than patients with obstructive CAD ($p < 0.0001$).

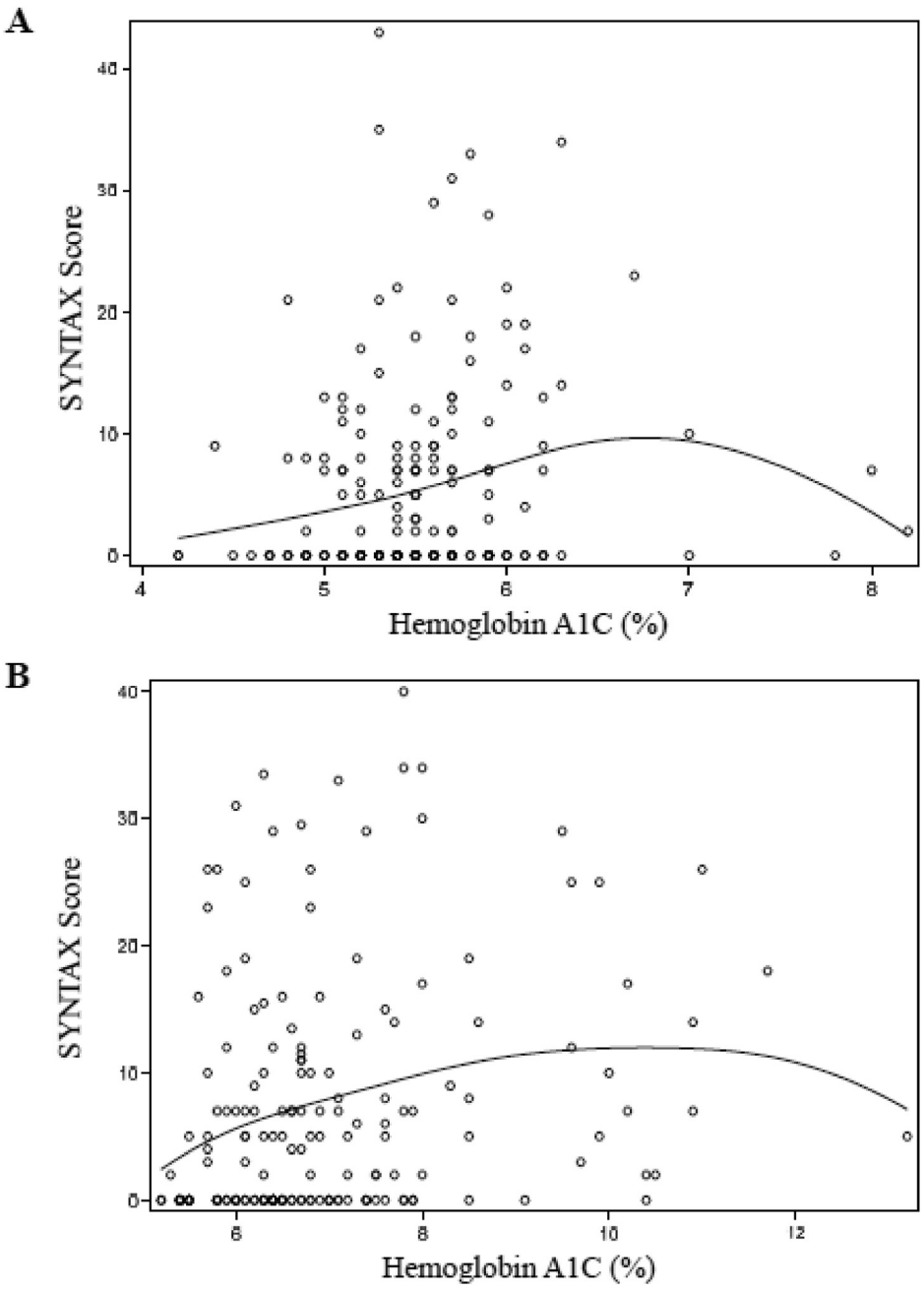

Fig. 4. HbA1c and SYNTAX score in diabetic and non-diabetic subjects. (a)- Plot of SYNTAX score vs HbA1c in diabetic subjects demonstrates a positive correlation ($p = 0.001$, $r = 0.29$). A penalized B-spline curve was used to fit the data points. (b)- Plot of SYNTAX score vs HbA1c in non-diabetic subjects demonstrates a positive correlation ($p = 0.01$, $r = 0.18$). A penalized B-spline curve was used to fit the data points.

Table 3
Potential predictors of obstructive CAD.

Variable	All patients		Non-DM		DM	
	N = 364		N = 190		N = 174	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Pentosidine	1.03 (0.99, 1.07)[a]	0.1539	1.05 (0.99, 1.11)[a]	0.0930	1.00 (0.94, 1.06)[a]	0.8751
CML	1.00 (0.98, 1.02)[b]	0.7464	1.01 (0.98, 1.04)[b]	0.4265	1.00 (0.97, 1.03)[b]	0.7685
sRAGE	1.03 (0.99, 1.04)[a]	0.3594	1.03 (0.99, 1.07)[a]	0.1108	1.00 (0.96, 1.03)[a]	0.8446
LDL	1.00 (0.99, 1.01)	0.8814	1.00 (0.99, 1.01)	0.5658	1.00 (0.99, 1.01)	0.9195
HbA1c	1.68 (1.36, 2.09)	<0.0001	1.88 (1.05, 3.37)	0.0335	1.83 (1.33, 2.52)	0.0002

OR: Odds ratio, CI: Confidence interval.
[a] Odds ratio for a 100-unit increase in pentosidine/sRAGE level.
[b] Odds ratio for a 10-unit increase in CML level.

Table 4
Correlation between factors.

Variable	Pentosidine	CML	sRAGE	LDL	HbA1c
	ρ_S (P-value)	ρ_S (P-value)	ρ_S (P-value)	ρ_S (P-value)	ρ_S (P-value)
Pentosidine	–				
CML	−0.10 (0.07)	–			
sRAGE	−0.14 (0.01)	0.14 (0.01)	–		
LDL	−0.05 (0.37)	−0.07 (0.22)	0.04 (0.45)	–	
HbA1c	0.07 (0.210	−0.06 (0.27)	−0.11 (0.04)	−0.10 (0.06)	–

ρ_S: Spearman correlation coefficient.

We analyzed only two of the many AGEs along with their soluble receptor. It is important to note that circulating AGE levels do not sufficiently reflect the AGE levels stored in the body's tissues [38]. Circulating concentrations of AGEs fluctuate over time and are affected by their renal and hepatic clearance [39]. To minimize this limitation, we excluded patients with renal and hepatic dysfunction, though inherent variations in function may lead to some discrepancies in the measured AGE levels. Furthermore, diet and medications can affect AGE and sRAGE levels [40,41]. For instance, treatment with statins has been associated with a reduction in AGE accumulation and an increase in sRAGE [42].

5. Conclusion

In patients with CAD undergoing elective cardiac catheterization, circulating pentosidine, CML, and sRAGE levels do not correlate with the presence of obstructive CAD or the SYNTAX score and SYNTAX score II regardless of diabetic status. Instead, the presence of CAD and the SYNTAX scores correlate positively with HbA_{1c} in individuals with and without diabetes.

CRediT authorship contribution statement

Craig Basman: Conceptualization, Methodology, Data curation, Writing - original draft, Investigation. **Sarah L. Fishman:** Investigation, Writing - original draft, Writing - review & editing, Visualization. **Dimiter Avtanski:** Investigation, Data curation, Validation, Methodology. **Umar Rashid:** Investigation. **Arber Kodra:** Investigation. **Karin Chen:** Investigation. **Rebecca Jonas:** Investigation. **Guillaume J. Stoffels:** Formal analysis, Visualization. **Martin Lesser:** Formal analysis, Visualization. **Damian Inlall:** Investigation. **Karina Ziskovich:** Methodology, Resources, Conceptualization, Project administration. **Varinder Singh:** Supervision, Conceptualization, Methodology, Investigation. **Leonid Poretsky:** Writing - original draft, Writing - review & editing, Supervision, Conceptualization, Methodology, Funding acquisition.

Declaration of competing interest

Varinder Singh is a consultant for Abbott, Boston Scientific, and Medtronic. None of the other authors have any conflicts of interest or disclosures at this time.

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[None]

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.metop.2020.100050.

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