2020

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

C. Basman

S. L. Fishman

D. Avtanski

U. Rashid

A. Kodra
Northwell Health

See next page for additional authors

Metabolism Open 7 (2020) 100050

Contents lists available at ScienceDirect

Metabolism Open

journal homepage: www.journals.elsevier.com/metabolism-open

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

Craig Basman [a], Sarah L. Fishman [b], Dimiter Avtanski [b], Umar Rashid [a], Arber Kodra [a], Karin Chen [b], Rebecca Jonas [c], Guillaume J. Stoffels [d], Martin Lesser [d], Damian Inlall [b], Karina Ziskovich [b], Varinder Singh [a], Leonid Poretsky [b, *]

[a] Department of Cardiovascular Medicine, Lenox Hill Hospital, Northwell Health, New York, NY, USA
[b] Division of Endocrinology and Friedman Diabetes Institute, Lenox Hill Hospital, Northwell Health, New York, NY, USA
[c] Department of Internal Medicine, Lenox Hill Hospital, Northwell Health, New York, NY, USA
[d] Biostatics Unit, Feinstein Institute for Medical Research, Northwell Health, Hempstead, NY, USA

ARTICLE INFO

Article history:
Received 30 April 2020
Received in revised form
8 July 2020
Accepted 7 August 2020
Available online 16 August 2020

Keywords:
Advanced glycation endproducts
Coronary artery disease
Diabetes mellitus
Hemoglobin A1C

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.

* Corresponding author. Lenox Hill Hospital, 110 East 59th St, Suite 3B, New York, NY, 10021, USA.
E-mail address: lporetsky@northwell.edu (L. Poretsky).

https://doi.org/10.1016/j.metop.2020.100050

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].

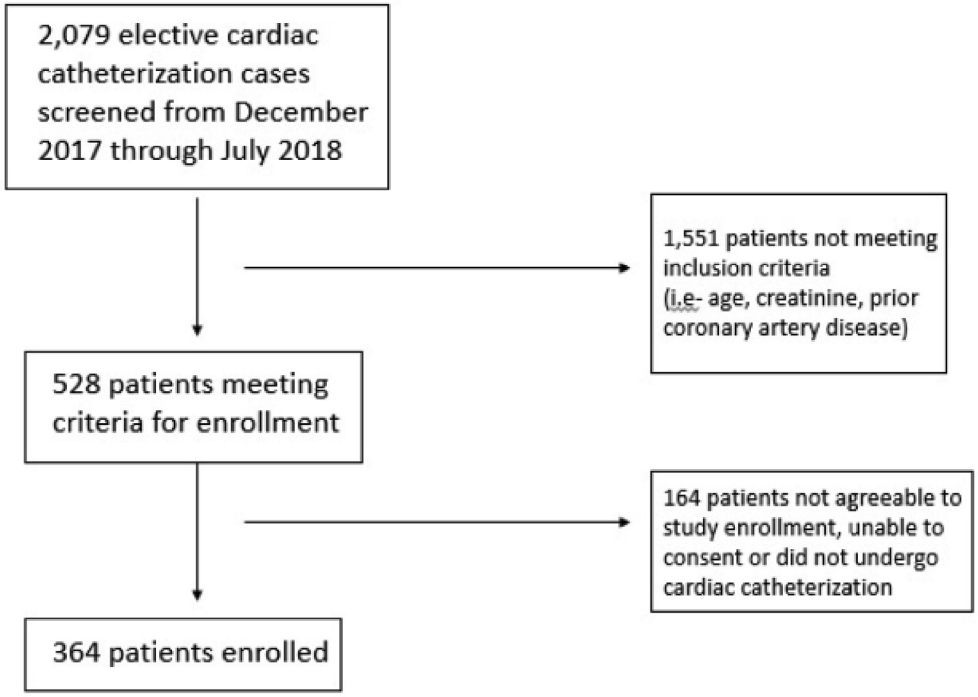

Fig. 1. Patient selection.

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.

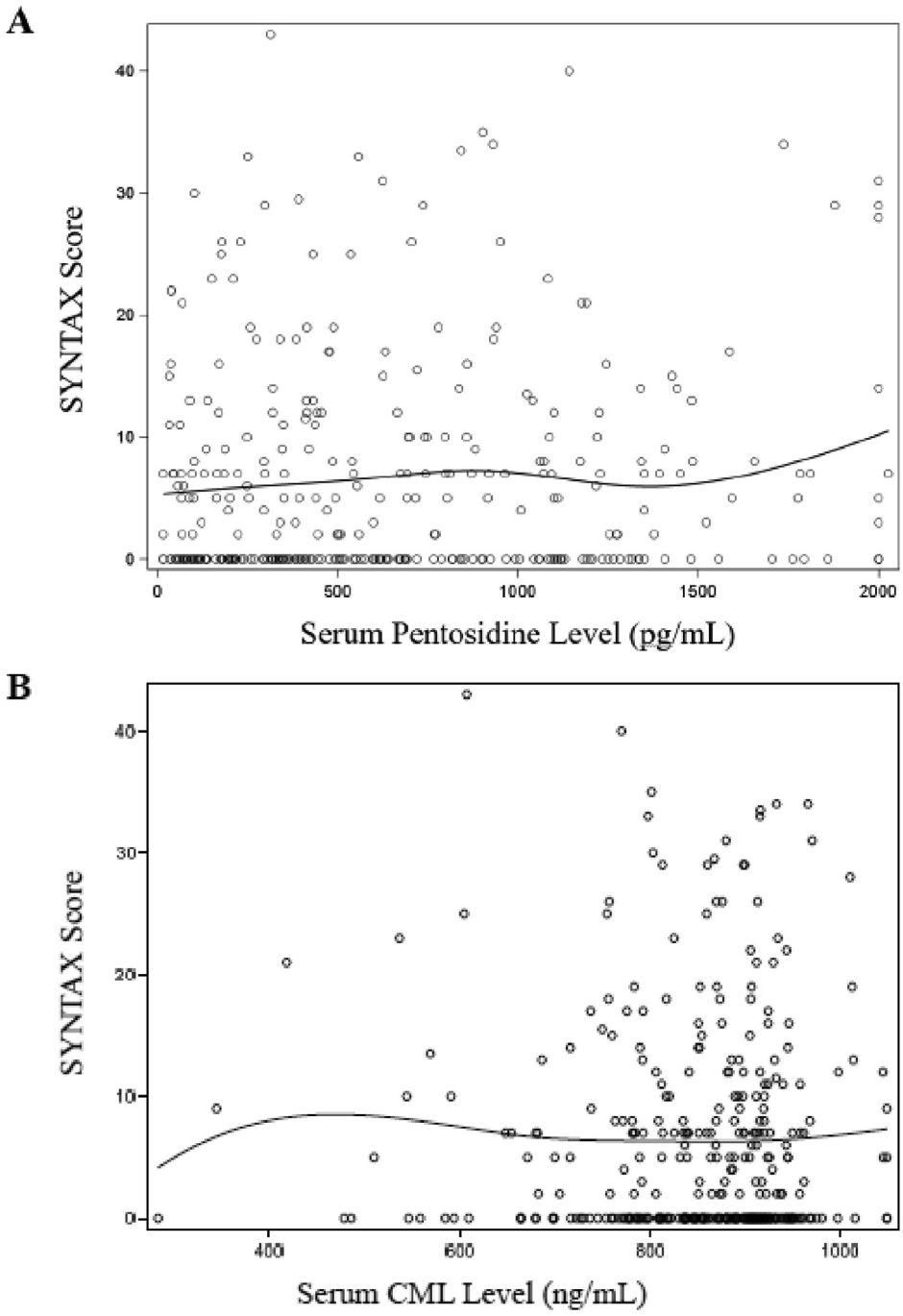

Fig. 2. Relationship of Advanced Glycation End-Products and Coronary Artery Disease. (A) No significant correlation of pentosidine levels and SYNTAX score. A penalized B-spline curve was used to fit the data points. (B) No significant correlation of CML levels and SYNTAX score. A penalized B-spline curve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

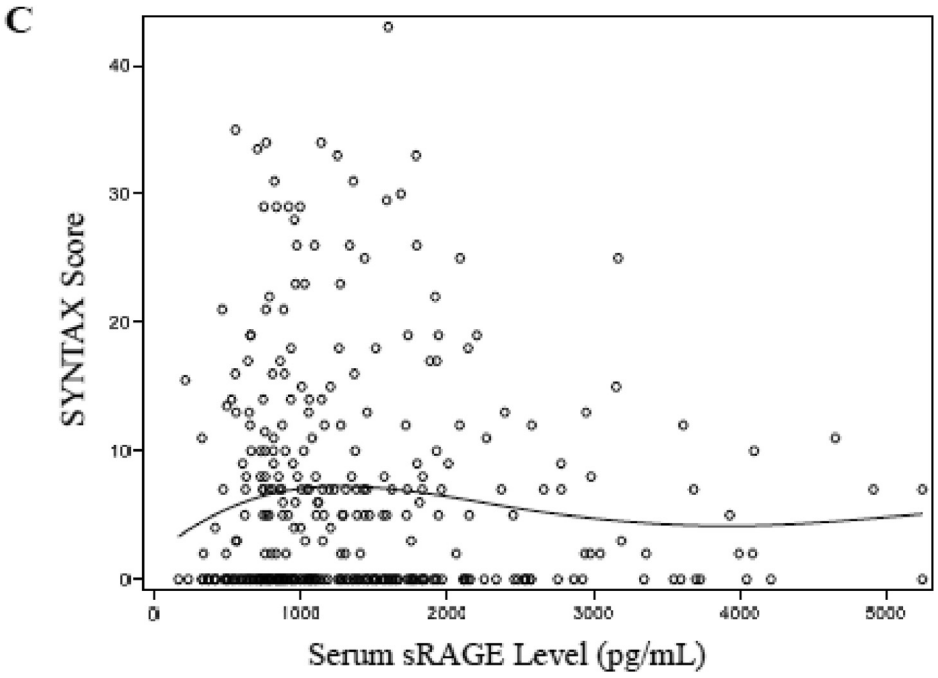

Fig. 2. (*continued*).

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

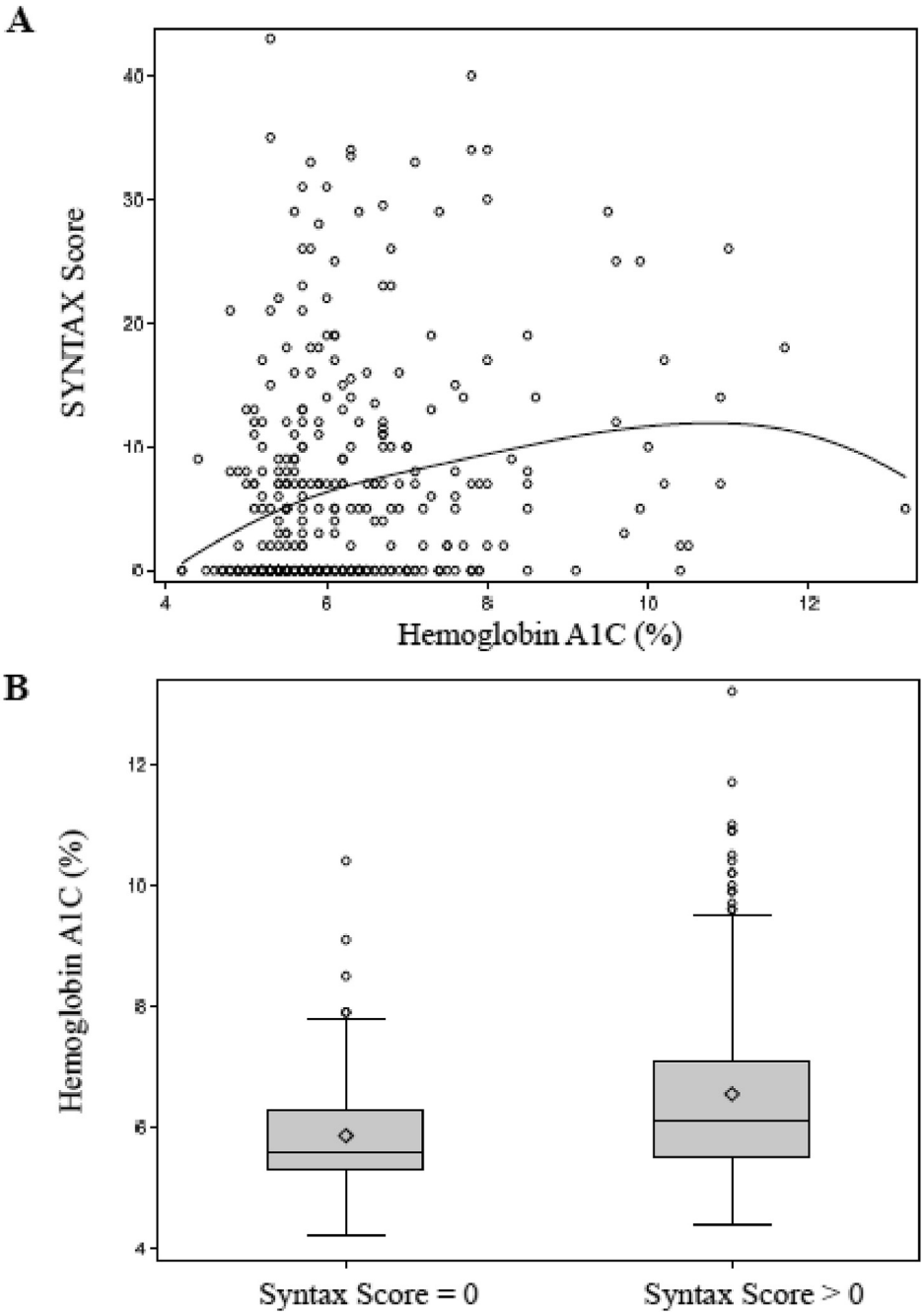

Fig. 3. Relationship of HbA1c and SYNTAX score. (A)- A positive correlation between HbA1c and the SYNTAX score ($p < 0.0001$, $r = 0.26$). A penalized B-spline curve was used to fit the data points.(B)- Patients with nonobstructive or normal coronary arteries have a lower HbA1c than patients with obstructive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

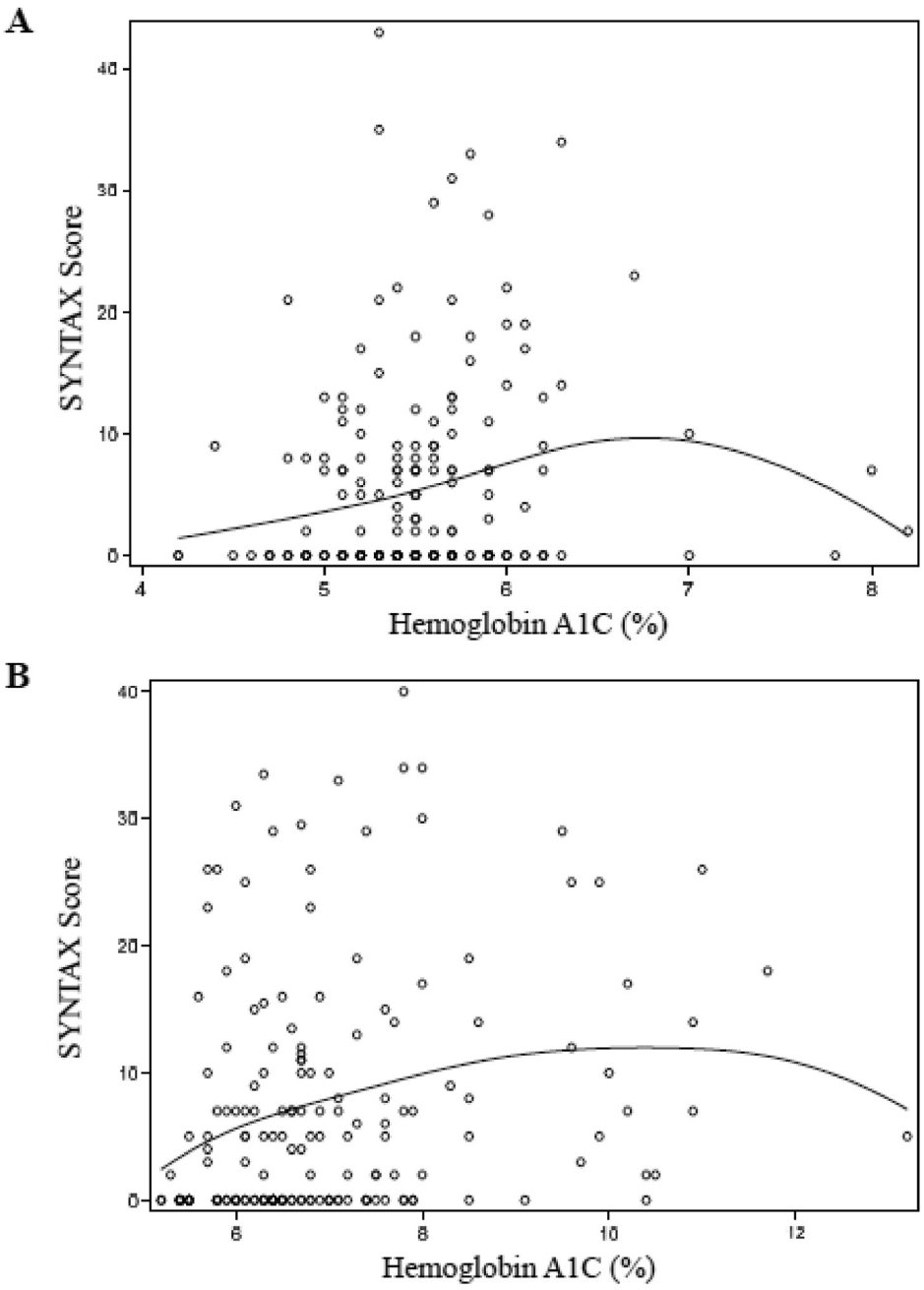

Fig. 4. HbA1c and SYNTAX score in diabetic and non-diabetic subjects. (a)- Plot of SYNTAX score vs HbA1c in diabetic subjects demonstrates a positive correlation ($p = 0.001$, $r = 0.29$). A penalized B-spline curve was used to fit the data points. (b)- Plot of SYNTAX score vs HbA1c in non-diabetic subjects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

Acknowledgements

[None]

Appendix A. Supplementary data

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

Funding source

This work was supported by grants from the Gerald G. and Dorothy R. Freidman New York Foundation for Medical Research and by the Empire Clinical Research Investigation Program of the New York State Department of Health.

References

[1] Action to Control Cardiovascular Risk in Diabetes Study Group, Gerstein HC, Miller ME, Byington RP, Goff Jr DC, Bigger JT, Buse JB, Cushman WC, Genuth S, Ismail-Beigi F, Grimm Jr RH, Probstfield JL, Simons-Morton DG, Friedewald WT. Effects of intensive glucose lowering in type 2 diabetes. NEJM 2008;358(24):2545–59.
[2] Advance Collaborative Group, Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, Marre M, Cooper M, Glasziou P, Grobbee D, Hamet P, Harrap S, Heller S, Liu L, Mancia G, Mogensen CE, Pan C, Poulter N, Rodgers A, Williams B, Bompoint S, de Galan BE, Joshi R, Travert F. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. NEJM 2008;358(24):2560–72.
[3] Duckworth W, Abraira C, Moritz T, Reda D, Emanuele N, Reaven PD, Zieve FJ, Marks J, Davis SN, Hayward R, Warren SR, Goldman S, McCarren M, Vitek ME, Henderson WG, Huang GD. VADT Investigators. Glucose control and vascular complications in veterans with type 2 diabetes. NEJM 2009;360(2):129–39.
[4] Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-Year follow-up of intensive glucose control in type 2 diabetes. NEJM 2008;359(15):1577–89.
[5] Hong LF, Li XL, Guo YL, Luo SH, Zhu CG, Qing P, Xu RX, Wu NQ, Li JJ. Glycosylated hemoglobin A1c as a marker predicting the severity of coronary artery disease and early outcome in patients with stable angina. Lipids Health Dis 2014;13:89.
[6] Garg N, Moorthy N, Kapoor A, Tewari S, Kumar S, Sinha A, Shrivastava A, Goel PK. Hemoglobin A1c in nondiabetic patients: an independent predictor of coronary artery disease and its severity. Mayo Clin Proc 2014;89(7):908–16.
[7] Tada Y, Yano S, Yamaguchi T, Okazaki K, Ogawa N, Morita M, et al. Advanced glycation end products-induced vascular calcification is mediated by oxidative stress: functional roles of NAD(P)H-oxidase. Horm Metab Res 2013;45(4):267–72.
[8] Kay AM, Simpson CL, Stewart JA. The role of AGE/RAGE signaling in diabetes-mediated vascular calcification. J Diabetes Res 2016;2016.
[9] Brownlee M, Cerami A, Vlassara H, Cerami A, Vlassara H. Advanced glycosylation end products in tissue and the biochemical basis of diabetic complications. NEJM 1988;318(20):1315–21.
[10] Zieman SJ, Kass DA. Advanced glycation end product crosslinking in the cardiovascular system: potential therapeutic target for cardiovascular disease. Drugs 2004;64(5):459–70.
[11] Prasad A, Bekker P, Tsimikas S. Advanced glycation end products and diabetic cardiovascular disease. Cardiol Rev 2012;20(4):177–83.
[12] Nin JW, Jorsal A, Ferreira I, Schalkwijk CG, Prins MH, Parving H. Higher plasma levels of advanced glycation end products are associated with incident cardiovascular disease and all-cause mortality in type 1 diabetes A 12-year follow-up study. Diabetes Care 2011;34(2):442–7.
[13] Kiuchi K, Nejima J, Takano T, Ohta M, Hashimoto H, Baxter GF. Increased serum concentrations of advanced glycation end products: a marker of coronary artery disease activity in type 2 diabetic patients. Heart 2001;85(1):87–91.
[14] Won KB, Chang HJ, Park GH, Hong SY, Jang Y, Chung N. High serum advanced glycation end-products predict coronary artery disease irrespective of arterial stiffness in diabetic patients. Kor Circ J 2012;42:335–40.
[15] Liu Y, Yang YM, Zhu J, Tan HQ, Liang Y, Li JD. Prognostic significance of hemoglobin A1c level in patients hospitalized with coronary artery disease. A systematic review and meta-analysis. Cardiovasc Diabetol 2011;10:98.
[16] Kerkeni M, Weiss IS, Jaisson S, Dandana A, Addad F, Gillery P, Hammami M. Increased serum concentrations of pentosidine are related to presence and severity of coronary artery disease. Thromb Res 2014;134(3):633–8.
[17] Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes DR, Mack MJ, Ståhle E, Feldman TE, van den Brand M, Bass EJ, Van Dyck N, Leadley K, Dawkins KD, Mohr FW. SYNTAX Investigators. Percutaneous coronary

intervention versus coronary-artery bypass grafting for severe coronary artery disease. NEJM 2009;360(10):961–72.
[18] Farooq V, van Klaveren D, Steyerberg EW, Meliga E, Vergouwe Y, Chieffo A, Kappetein AP, Colombo A, Holmes DRJr, Mack M, Feldman T, Morice MC, Stahle E, Onuma Y, Morel MA, Garcia-Garcia HM, van Es GA, Dawkins KD, Mohr FW, Serruys PW. Anatomical and clinical characteristics to guide decision making between coronary artery bypass surgery and percutaneous coronary intervention for individual patients: development and validation of SYNTAX Score II. Lancet 2013;381:639–50.
[19] Basta G, Berti S, Cocci F, Lazzerini G, Parri S, Papa A, et al. Plasma N-epsilon-(carboxymethyl)lysine levels are associated with the extent of vessel injury after coronary arterial stenting. Coron Artery Dis 2008;19(5):299–305.
[20] Fujisawa K, Katakami N, Kaneto H, Naka T, Takahara M, Sakamoto F, Irie Y, Miyashita K, Kubo F, Yasuda T, Matsuoka T, Shimomura I. Circulating soluble RAGE as a predictive biomarker of cardiovascular event risk in patients with type 2 diabetes. Atherosclerosis 2013;227:425–8. 2013.
[21] Stanislovatiene D, Zaliuniene D, Steponaviciute R, Zemaitiene R, Gustiene O, Zaliunas R. N-caroxymethllysine as a biomarker for coronary artery disease and age-related macular degeneration. Medicina 2016;52:99–103. 2016.
[22] Semba RD, Ferrucci L, Sun K, Beck J, Dalal M, Varadhan R, Walston J, Guralnik JM, Fried LP. Advanced glycation end products and their circulating receptors predict cardiovascular disease mortality in older community-dwelling women. Aging Clin Exp Res 2009 Apr;21(2):182–90.
[23] Yang ZK, Shen Y, Shen WF, Pu LJ, Meng H, Zhang RY. Elevated glycated albumin and reduced endogenous secretory receptor for advanced glycation endproducts levels in serum predict major adverse cardio-cerebral events in patients with type 2 diabetes and stable coronary artery disease. Int J Cardiol 2015;197:241–7.
[24] Sugiyama S, Miyata T, Ueda, Tanaka H, Maeda K, Kawashima S, Van Ypersele de Strihou C, Kurokawa K. Plasma levels of pentosidine in diabetic patients: an advanced glycation end product. J Am Soc Nephrol 1998;9(9):1681–8.
[25] Prasad K. Low levels of serum soluble receptor for advanced glycation end-products, biomarkers for disease state: myth or reality. Int J Angiol 2014;23(1):11–6.
[26] Colhoun H, Betteridge D, Durrington P, Hitman G, Neil A, Livingstone S, Charlton-Menys V, Bao W, DeMicco D, Preston G, Deshmukh H, Tan K, Fuller J. Total solube and endogeous secretory receptor for advanced glycation end-products as biomarkers of coronary heart disease risk in patients with type 2 diabetes. Diabetes 2016;60(9):2379–85.
[27] Saleem T, Mohammad KH, Abdel-Fattah MM, Abbasi AH. Association of glycosylated haemoglobin level and diabetes mellitus duration with the severity of coronary artery disease. Diabetes Vasc Dis Res 2008;5(3):184–9.
[28] Gustafsson I, Kistorp CN, James MK, Faber JO, Dickstein K, Hildebrandt PR. Unrecognized glycometabolic disturbance as measured by hemoglobin A1c is associated with a poor outcome after acute myocardial infarction. Am Heart J 2007;154(3):470–6.
[29] Cicek G, Uyarel H, Ergelen M, Ayhan E, Abanonu GB, Eren M, Gibson CM. Hemoglobin A1c as a prognostic marker in patients undergoing primary angioplasty for acute myocardial infarction. Coron Artery Dis 2011;22(3):131–7.
[30] Leong A, Chen J, Wheeler E, Hivert MF, Liu CT, Merino J, Dupuis J, Tai ES, Rotter JI, Florez JC, Barross I, Meigs JB. Mendelian randomization analysis of hemoglobin A1c as a risk factor for coronary artery disease. Diabetes Care 2019;42(1):1202–8.
[31] Riddle MC, Gerstein HC. The cardiovascular legacy of good glycemic control: clues about mediators from the DCCT/EDIC study. Diabetes Care 2019;42(7):1159–61.
[32] Berliner JA, Navab M, Fogelman AM, Frank JS, Demer LL, Edwards PA, Watson AD, Lusis AJ. Atherosclerosis: basic mechanisms. Oxidation, inflammation, and genetics. Circulation 1995;91(9):2488–96.
[33] Cholesterol Treatment Trialists' Collaborators. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. Lancet 2012;380(9841):581–90.
[34] Prospective Studies Collaboration, Lewington S, Whitlock G, Clarke R, Sherliker P, Emberson J, Halsey J, Qizilbash N, Peto R, Collins R. Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55,000 vascular deaths. Lancet 2007;370(9602):1829–39.
[35] Emerging Risk Factors C, Di Angelantonio E, Gao P, Pennells L, Kaptoge S, Caslake M, Thompson A, Butterworth AS, Sarwar N, Wormser D, Saleheen D, Ballantyne CM, Psaty BM, Sundström J, Ridker PM, Nagel D, Gillum RF, Ford I, Ducimetiere P, Kiechl S, Koenig W, Dullaart RP, Assmann G, D'agostino Sr RB, Dagenais GR, Cooper JA, Kromhout D, Onat A, Tipping RW, Gómez-de-la-Cámara A, Rosengren A, Sutherland SE, Gallacher J, Fowkes FG, Casiglia E, Hofman A, Salomaa V, Barrett-Connor E, Clarke R, Brunner E, Jukema JW, Simons LA, Sandhu M, Wareham NJ, Khaw KT, Kauhanen J, Salonen JT, Howard WJ, Nordestgaard BG, Wood AM, Thompson SG, Boekholdt SM, Sattar N, Packard C, Gudnason V, Danesh J. Lipid-related markers and cardiovascular disease prediction. J Am Med Assoc 2012;307(23):2499–506.
[36] Cholesterol Treatment Trialists' (Ctt) Collaboration, Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhala N, Peto R, Barnes EH, Keech A, Simes J, Collins R. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. Lancet 2010;376(9753):1670–81.
[37] Gan T, Liu X, Xu G. Glycated albumin versus HbA1c in the evaluation of glycemic control in patients with diabetes and CKD. Kidney Int Rep 2017;3(3):542–54.
[38] Giardino I, Edelstein D, Brownlee M. Nonenzymatic glycosylation in vitro and in bovine endothelial cells alters basic fibroblast growth factor activity. A model for intracellular glycosylation in diabetes. J Clin Invest 1994;94:110–1.
[39] De Vos LC, Lefrandt JD, Dullaart RP, Zeebregts CJ, Smit AJ. Advanced glycation end products: an emerging biomarker for adverse outcome in patients with peripheral artery disease. Atheroclerosis 2016, November;254:291–9.
[40] Fishman SL, Sonmez H, Basman C, Singh V, Poretsky L. The role of advanced glycation end-products in the development of coronary artery disease in patients with and without diabetes mellitus: a review. Mol Med 2018;24(1):59.
[41] Uribarri J, Woodruff S, Goodman S. Advanced glycation end products in foods and a practical guide to their reduction in the diet. J Am Diet Assoc 2010;110(6):911–6.
[42] Lu L, Peng W, Wang W, Wang L, Chen Q, Shen W. Effects of atorvastatin on progression of diabetic nephropathy and local RAGE and soluble RAGE expressions in rats. J Zhejiang Univ Sci B 2011 Aug;12(8):652–9 [Internet].