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Advanced glycation endproduct carboxymethyl-lysine and risk of incident peripheral artery disease in older adults: The Cardiovascular Health Study

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Abstract

Carboxymethyl-lysine (CML) is an advanced glycation end products that is detectable in the serum. Higher CML levels have been associated with increased risk of coronary heart disease, stroke, and cardiovascular mortality. We determined whether high CML levels are also associated with risk of peripheral artery disease (PAD) in Cardiovascular Health Study (CHS) participants who were all 65 years of age and older at baseline. Multi-variate Cox proportional hazards models were used to determine the association of baseline CML levels with incident PAD in 3,267 individuals followed for a median length of 10.0 years. 157 cases of incident PAD occurred during follow-up. No significant relationship between CML and risk of PAD was found (hazard ratio per standard deviation increment=1.03; 95% confidence interval 0.87, 1.23).

Keywords

Advanced glycation end products; Ankle brachial index; Inflammation; Peripheral artery disease

Advanced glycation end products (AGEs) are implicated in atherogenesis through both non-receptor-mediated and receptor-mediated pathways which lead to macrophage activation, pro-inflammatory cytokine release, smooth muscle cell proliferation, and impaired endothelial function.[1] While various different AGEs are known to exist in the circulation, carboxymethyl-lysine (CML) is the most well-studied. Higher serum CML levels have already been associated with coronary heart disease and stroke in older adults.[2] Given known differences in risk factors between vascular beds, we determined whether high CML levels are also associated with risk of peripheral artery disease (PAD).

The Cardiovascular Health Study (CHS) is a community-based, longitudinal study of 5,888 individuals 65 years of age and older. Eligible participants were those without PAD and who had CML measured at year 9 (1996–1997), which served as the baseline for this study. CML measurement was performed in 2011 with an immunoassay (AGE-CML ELISA, Microcoat, Penzberg, Germany) in serum specimens stored at −70 °C since collection in 1996–1997.

The ankle-brachial index (ABI) was assessed at year 11 (1998–1999) and the measurement protocol has been described previously.[3] A low ABI was defined as a value of 0.9 or less. An ABI>1.4 was defined as a non-compressible vessel. Clinical PAD was identified by self-report, review of medical records for other events, or as review of CMS records for the ICD-9 codes 440.2 and 443.9 and adjudicated by the cardiac subgroup of the CHS Clinical Events Subcommittee. Detailed criteria for meeting a diagnosis of clinical PAD have already been described.[3] Follow-up data for clinical PAD was available thru June 2015.

Individuals who did not attend the Year 9 visit (n=1475), had prevalent clinical PAD at Year 9 (n=106), or were missing CML measurement (n=1040) were excluded from the analysis. Additionally, those without ABI measurement or with non-compressible vessels were excluded from the low ABI analysis (n=984). Logistic regression modeling was performed to investigate the associations of baseline CML levels with low ABI at Year 11. Cox proportional hazards models were used to determine the association of baseline CML levels with incident PAD. In these analyses, CML was modeled continuously (per 1 standard deviation (SD) increment) and also categorized into quartiles. Models were adjusted for age, sex, race, clinic site, total cholesterol, myocardial infarction, stroke, heart failure, anti-hypertension medication use, systolic blood pressure, cigarette smoking status and pack-years, diabetes medication use, glucose, physical activity, statin use, estimated glomerular filtration rate, albumin, and c-reactive protein.

Mean age for included participants was 78.0 years, 39% were male, and 16% were black. There were 417 (17.2%) participants found to have a low ABI at Year 11. Over a median follow-up of 10.0 years, 157 (4.8%) participants developed clinical PAD. No significant relationship between CML levels and risk of either prevalent low ABI or incident clinical PAD was found (Table).

In a large community-based cohort of older adults, we found no association of CML levels with either an increased risk of low ABI or incident clinical PAD in multivariate adjusted models. Current literature regarding associations of CML and PAD were limited to small case-control studies that measured tissue AGE with skin autofluorescence, showing higher levels in those with PAD compared to those without.[4] Atherosclerosis is a complex process that demonstrates heterogeneity in different-sized vascular beds. Significant differences in the strength of the association of traditional cardiovascular risk factors such as diabetes or cigarette smoking with PAD versus other forms of atherosclerotic disease have already been established.[5] It is possible, therefore, that the relationship of CML with the larger vessels of the lower extremities may differ from its relationship with other smaller arterial vessels located in the coronary or cerebral vasculature. Additionally, it is also possible that the relationship of CML in the development of PAD may also differ with age and that a role for this AGE may exist in younger individuals. Participants in this cohort have had over 70 years to develop PAD through multiple pathways and elevated CML levels found late in life may not be significant enough to make a difference.

Our study has limitations. Eligibility for this analysis required that participants be healthy enough to attend the Year 9 visit and have CML measured at this time. ABI examination was not performed at the same time of CML measurement.

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Table.

Associations between carboxymethyl-lysine levels (pmol/l) and peripheral artery disease[a]

Prevalent low ABI (n=12425)				
	Cases of low ABI	**Model 1[b]**	**Model 2[c]**	
		OR (95% CI)	**OR (95% CI)**	
1st quartile (≤497.7)	109	1.00 (Referent)	1.00 (Referent)	
2nd quartile (497.7–582.6)	116	1.12 (0.83, 1.51)	1.12 (0.81–1.54)	
3rd quartile (>582.6–700.6)	87	0.75 (0.55, 1.03)	0.71 (0.50–1.01)	
4th quartile (>700.6)	105	1.01 (0.75, 1.38)	0.96 (0.68–1.35)	
Per SD (215)		1.03 (0.92, 1.14)	0.99 (0.88–1.12)	
Incident clinical PAD (n=3267)				
	Cases of incident clinical PAD	**Incidence Rate[d] (95% CI)**	**Model 1[b]**	**Model 2‡**
			HR (95% CI)	**HR (95% CI)**
1st quartile (≤497.7)	43	4.74 (3.52, 6.40)	1.00 (Referent)	1.00 (Referent)
2nd quartile (497.7–582.6)	40	4.69 (3.44, 6.40)	0.95 (0.62, 1.47)	1.11 (0.70, 1.74)
3rd quartile (>582.6–700.6)	47	5.57 (4.19, 7.42)	1.13 (0.74, 1.71)	1.18 (0.76, 1.86)
4th quartile (>700.6)	27	3.61 (2.48, 5.27)	0.70 (0.43, 1.15)	0.79 (0.47, 1.35)
Per SD (215)			1.01 (0.84, 1.21)	1.03 (0.87, 1.23)

[a] Results of logistic regressions models (prevalent low ABI) and proportional hazards models (incident clinical PAD) are shown for CML levels by quartiles of the distribution, with each CML quartile compared with the 1st quartile (referent quartile), and per standard deviation increment

[b] Model 1 adjusted for age (years), male sex, race, clinic site

[c] Model 2 adjusted for Model 1 + systolic blood pressure, anti-hypertensive medications, smoking status and pack-years, physical activity, total cholesterol, fasting glucose, albumin, c-reactive protein, estimated glomerular filtration rate, diabetes medications, anti-hypertensive use, statin use, prevalent myocardial infarction, prevalent heart failure, and prevalent stroke

[d] Rates are per 1000 person years