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Amyloid-beta (1–40) Peptide and Subclinical Cardiovascular Disease

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Amyloid-beta (1–40) (Aβ40), a peptide with pro-inflammatory and pro-atherosclerotic properties is associated with arterial aging (1) and with major adverse cardiovascular events in patients with stable coronary heart disease (CHD), heart failure or acute coronary syndrome (1–3). However, the clinical significance of Aβ40 in general population without clinically overt cardiovascular disease (CVD) is unknown. We sought to determine the association of the circulating Aβ40 levels with facets of subclinical cardiac and coronary artery disease in the general population.

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Aβ40 was measured in plasma probes by a well-characterized enzyme linked immunosorbent assay (ELISA) (Invitrogen, CA, USA) (1,3) from participants in the Dallas Heart Study-Phase 2 (DHS-2) population (4) who did not have clinically overt CVD. In addition to medical history, daily activity was assessed by a single axis accelerometer (ActiGraph model 7164, LLC, Pensacola, Florida) and maximum oxygen consumption (VO_2max) was measured during sub-maximal treadmill exercise test. Subclinical cardiovascular disease was assessed by: (a) markers of cardiac function and structure by cardiovascular magnetic resonance imaging (cMRI, Achieva, Philips Medical Systems, Best, The Netherlands); (b) coronary artery calcium (CAC) by computed tomography (Imatron Inc., San Bruno, California); (c) N-terminal pro-brain natriuretic peptide (NT-proBNP) (Elecsys proBNP immonoassay Roche Diagnostics, Indianapolis, Indiana); (d) high sensitivity cardiac troponin T (hs-cTnT) (Elecsys-2010 Troponin T hs STAT Immunoassay, Roche Diagnostics, Indianapolis, Indiana). The University of Texas Southwestern Medical Center Institutional Review Board approved the study, and all participants provided written informed consent.

The study population included 3,266 participants with a mean age of 49.6 years, 59.5% female, 48.8% black, with prevalence of smoking 21.6%, arterial hypertension 48.5%, hypercholesterolemia 25.9% and diabetes mellitus 14.4%. Among these individuals, 34.4% were on anti-hypertensive and 16.1% on statin treatment. In univariable analyses, Aβ40 was positively associated with increasing age, non-black race, diabetes mellitus and hypercholesterolemia, triglycerides levels, pulse pressure and daily sedentary time, and inversely associated with diastolic blood pressure, duration of daily moderate to vigorous activity and estimated glomerular filtration rate (eGFR) ($P<0.05$ for all). After multivariable adjustment for all variables univariably correlated with Aβ40, Aβ40 remained associated with age (standardized beta = 0.075, P=0.001), non-black race ($\beta = -0.07$, P = 0.001), triglyceride levels ($\beta = 0.047$, P = 0.02) and eGFR ($\beta = -0.124$, $P<0.001$).

Subsequently, we investigated associations of plasma Aβ40 with markers of subclinical CVD and cardiorespiratory fitness. Aβ40 was associated with increasing CAC, NT-proBNP, hs-cTnT and with decreasing left ventricular (LV) end-systolic volume, LV stroke volume index and VO_2 max (Table 1). After multivariable adjustment for traditional cardiovascular risk factors, race, eGFR and hsCRP, Aβ40 was independently associated with NT-proBNP, hs-cTnT, left atrial emptying fraction and VO_2 max (Table 1). Finally, full adjustment for traditional risk factors, renal function, hs-CRP, education level, yearly income and microalbuminuria, revealed that Aβ40 remained significantly associated with NT-proBNP and VO_2 max (Table 1). Aβ40 also correlated with high CAC score but significance was lost after adjusting for age and eGFR (Table 1).

In summary, plasma Aβ40 is associated with cumulative risk factor profile with aging, renal dysfunction, non-black race and the level of triglycerides being the major independent determinants of its variability in the general population without clinically overt CVD. Most importantly, we report here that Aβ40 is associated with subclinical cardiac disease as evidenced by the positive association with the cardiac stress and injury markers NT-proBNP and hs-cTnT, irrespectively of traditional cardiovascular risk factors, renal function and systemic inflammation. Increased circulating NT-proBNP is indicative of increased LV

stretch and filling pressures while increased hs-TnT may reflect subclinical myocardial damage in subjects without overt CHD (4). Interestingly, Aβ40 remained associated with NT-proBNP and VO_2 max even after considering an additional multivariable model with full demographic characteristics of the population, arterial blood pressure, blood lipid profile and urine microalbumin levels as a marker of early renal and vascular dysfunction. Given that the cytotoxic Aβ40 peptide accumulates in heart tissues (5) and is independently associated with lower cardiorespiratory fitness in our study, our findings support the notion that plasma Aβ40 may reflect both cardiovascular aging and health status in general population. Further prospective studies are warranted to evaluate the prognostic value of plasma Aβ40 levels for the development of CVD and cardiovascular events in general population.

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Table 1.

Univariable and multivariable associations of Aβ40 with subclinical cardiovascular disease and cardiorespiratory fitness

Dependent variable	Univariable analysis	Multivariable analysis (Model 1)	Multivariable analysis (Model 2)
LV mass index, g/m2	−0.04 (0.09)	−0.003 (0.88)	−0.016 (0.48)
LV SVI, m1/m2	**−0.057 (0.02)**	−0.014(0.59)	−0.028 (0.28)
LVEF, %	0.008 (0.741)	−0.022 (0.40)	−0.017 (0.55)
LA emptying fraction, %	−0.049 (0.06)	**−0.067 (0.03)**	−0.065 (0.08)
*hs-cTnT, pg/ml	**0.067 (0.002)**	**0.041 (0.04)**	0.026 (0.21)
NT-proBNP, pg/ml	**0.141 (<0.001)**	**0.088 (<0.001)**	**0.067 (0.001)**
*CAC, Agatston units	**0.062 (0.001)**	−0.001 (0.98)	0.009 (0.65)
Treadmill VO_2 max, ml/kgr per min	**−0.058 (0.002)**	**−0.044 (0.02)**	**−0.045 (0.02)**

Numbers indicate standardized beta coefficient and numbers in parentheses indicate P value, by linear regression analysis. Standardized coefficient represents the number of standard deviations the dependent variable will change per one standard deviation increase in Aβ40.

*indicates log transformed dependent variables.

Multivariable Model 1 includes age, gender, black race, hypertension, diabetes mellitus, smoking, hyperlipidemia, body mass index, hsCRP and estimated glomerular filtration rate.

Multivariable Model 2 includes age, gender, black race, education status, income, LDL, SBP, DBP diabetes mellitus, triglycerides, smoking, body mass index, hsCRP, microalbuminuria and estimated glomerular filtration rate.

In 15 subjects (0.49% of the population) Aβ40 concentrations were lower than the detection limit (<6pg/ml) of the ELISA used.

Abbreviations: Aβ40, amyloid beta 1–40 peptide; GFR, estimated glomerular filtration rate by the MDRD formula; VO_2max, maximum oxygen consumption; LV, left ventricular; SVI, stroke volume index; LVEF, left ventricle ejection fraction; LA, left atrium; CAC, coronary artery calcium score; hs-cTnT, high sensitivity troponin T; NT-proBNP, N-terminal pro-brain natriuretic peptide; SBP, systolic blood pressure; DBP, diastolic blood pressure; hsCRP, high sensitivity C-reactive protein;