VOL. 72, NO. 9, 2018
ISSN 0735-1097/$36.00

Letters

Amyloid-Beta (1-40) Peptide and Subclinical Cardiovascular Disease

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

Aβ40 was measured in plasma probes by a well-characterized enzyme-linked immunosorbent assay (ELISA) (Invitrogen, Carlsbad, California) (1,3) from participants in the DHS-2 (Dallas Heart Study-Phase 2) study 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, ActiGraph, Pensacola, Florida), and maximum oxygen consumption (Vo_2 max) was measured during a submaximal treadmill exercise test. Subclinical cardiovascular disease was assessed by: 1) markers of cardiac function and structure by cardiovascular magnetic resonance imaging (Achieva, Philips Medical Systems, Best, the Netherlands); 2) coronary artery calcium (CAC) by computed tomography (Imatron, San Bruno, California); 3) N-terminal pro-B-type natriuretic peptide (NT-proBNP) (Elecsys proBNP immunoassay, Roche Diagnostics, Indianapolis, Indiana); and 4) high-sensitivity cardiac troponin T (hs-cTnT) (Elecsys-2010 Troponin T hs STAT Immunoassay, Roche Diagnostics). 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 a prevalence of smoking 21.6%, arterial hypertension 48.5%, hypercholesterolemia 25.9%, and diabetes mellitus 14.4%. Among these individuals, 34.4% were on antihypertensive agents and 16.1% were 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, and hs-cTnT, and with decreasing left ventricular (LV) end-systolic volume, LV stroke volume index, and Vo_2 max (Table 1).

TABLE 1 Univariable and Multivariable Associations of Aβ40 With Subclinical CVD and Cardiorespiratory Fitness

Dependent Variable	Univariable Analysis	Multivariable Analysis (Model 1)	Multivariable Analysis (Model 2)
LV mass index, g/m^2	−0.04 (0.09)	−0.003 (0.88)	−0.016 (0.48)
LV SVI, ml/m^2	**−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/kg/min	**−0.058 (0.002)**	**−0.044 (0.02)**	**−0.045 (0.02)**

Values are standardized beta coefficient (p value), by linear regression analysis. Standardized coefficient represents the number of standard deviations the dependent variable will change per 1 SD increase in Aβ40. Values in **bold** are statistically significant. Multivariable Model 1 includes age, sex, black race, hypertension, diabetes mellitus, smoking, hyperlipidemia, body mass index, hsCRP, and estimated glomerular filtration rate. Multivariable Model 2 includes age, sex, 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 (<6 pg/ml) of the enzyme-linked immunosorbent assay used. *Indicates log-transformed dependent variables.

Aβ40 = amyloid beta 1-40 peptide; CAC = coronary artery calcium score; CVD = cardiovascular disease; DBP = diastolic blood pressure; GFR = estimated glomerular filtration rate by the MDRD formula; HDL = high-density lipoprotein; hsCRP = high-sensitivity C-reactive protein; hs-cTnT = high-sensitivity troponin T; LA = left atrium; LDL = low-density lipoprotein; LV = left ventricular; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide; SBP = systolic blood pressure; SVI = stroke volume index; Vo_2 max = maximum oxygen consumption.

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, hsCRP, 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 a high CAC score, but significance was lost after adjusting for age and eGFR (**Table 1**).

In summary, plasma Aβ40 is associated with a 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, irrespective of traditional cardiovascular risk factors, renal function, and systemic inflammation. Increased circulating NT-proBNP is indicative of increased LV stretch and filling pressures, whereas increased hs-TnT may reflect subclinical myocardial damage in subjects without overt coronary heart disease (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 the general population.

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https://doi.org/10.1016/j.jacc.2018.06.027

Please note: The salaries of Drs. Pol and Drosatos were covered by my NIH R01 grant. Dr. Brilakis has received consulting/speaker honoraria from Abbott Vascular, ACIST, the American Heart Association (associate editor of *Circulation*), Amgen, Asahi, Cardiovascular Innovations Foundation (board of directors), CSI, Elsevier, GE Healthcare, Medicure, Medtronic, and Nitiloop; and has received research support from Boston Scientific and Osprey. Dr. de Lemos has received grant support from Abbott Diagnostics; and has been a consultant for Abbott Diagnostics, Roche Diagnostics, Ortho Clinical Diagnostics, and Quidel Cardiovascular, Inc. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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Human Cardiac Fibroblasts Engage the Sarcoplasmic Reticulum in Induced Pluripotent Stem Cell-Derived Cardiomyocyte Excitation–Contraction Coupling

Ca^{2+}-induced Ca^{2+} release (CICR), the process whereby a small influx of Ca^{2+} across the sarcolemma triggers a significantly larger Ca^{2+} release from the sarcoplasmic reticulum (SR), is at the heart of efficient cardiac excitation-contraction coupling (ECC). This process is rudimentary in neonatal cardiomyocytes and significantly diminished in many forms of cardiac disease (1). As such, SR regulation has long been a potential therapeutic target of great interest.