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Association between serum activin A and metabolic syndrome in older adults: Potential of activin A as a biomarker of cardiometabolic disease

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ABSTRACT

Cardiovascular disease imposes substantial burdens of morbidity and mortality that increase with population aging. Estimating cardiometabolic risk accurately and expediently is challenging, and no single biomarker is satisfactory; hence, we investigated the potential of serum activin A for this purpose. Study data were collected from 433 community-dwelling adults age ≥53 years from Yilan County, Taiwan. Data included: demographics and medical history; physical measurements (blood pressure, body mass index, waist circumference); comprehensive functional assessments (frailty, cognitive function, depressive symptoms, nutritional status); fasting blood biochemistry (glucose, high-density lipoprotein cholesterol, triglycerides, high-sensitivity C-reactive protein, insulin-like growth factor-1, activin A, stratified into high, medium and low tertiles, and others); and dual-energy X-ray absorptiometry. Metabolic syndrome was considered a proxy for overall cardiometabolic risk. Subjects mean age was 69.3 ± 9.2 years, 48.3% were males. Compared to women, men had higher systolic blood pressure, education levels, relative appendicular skeletal muscle mass, waist circumference, physical activity, walking speed, free androgen index, and levels of serum uric acid, alanine aminotransferase, and dehydroepiandrosterone sulfate. High activin A was significantly associated with age, relative appendicular skeletal muscle mass in both gender, waist circumference in women, current alcohol drinking, hypertension, and Charlson Comorbidity Index. There were dose-dependent relationships (low to high) between serum activin A and frailty, cognitive impairment, malnutrition, metabolic syndrome, uric acid, and high-sensitivity C-reactive protein. Logistic regression analyses showed older age, serum uric acid, and metabolic syndrome were significantly associated with medium and high activin-A status, whereas, skeletal muscle mass, insulin-like growth factor-1 and dehydroepiandrosterone sulphate were associated with high, but not medium, serum activin A. This discovery of a dose-dependent association between serum activin A levels, age, and metabolic syndrome, suggests activin A may be a biomarker of overall cardiometabolic risk; however, further studies are needed to evaluate its potential applications in assessing and managing cardiometabolic risk.

1. Introduction

Population aging is a global phenomenon posing unique challenges to healthcare systems (Lu et al., 2016; Dall et al., 2013). Despite disability being considered a stronger predictor for mortality than for multimorbidity in older adults (Landi et al., 2010), cardiovascular disease also plays an important role in the clinicopathology of age-related disability, dementia, or mortality (Mukamal et al., 2018; Lourenco et al., 2018). Components of cardiometabolic risk may act not only independently but also in clusters, worsening their detrimental health impacts (Said et al., 2016). A cluster of multiple cardiometabolic risk factors, collectively designated metabolic syndrome, may better identify people at increased risk for developing cardiovascular disease or diabetes mellitus (Ardern and Jassen, 2007), although the prognostic

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role of metabolic syndrome in older adults remains controversial (Mozaffarian et al., 2008); major confounding effects in older people may be attributable to the 'obesity paradox' (Kim et al., 2016). Nevertheless, metabolic syndrome itself, or the sum of its components, still provides an excellent benchmark of cardiometabolic risk. Although metabolic syndrome (or its components) may reflect overall cardiometabolic risk, multiple measurements are required to confirm this diagnosis. Therefore, a unitary biomarker of chronic inflammation, insulin resistance, dyslipidemia, and high blood pressure, may enable earlier identification of people at high cardiometabolic risk, and timely intervention.

Activin A is a member of the transforming growth factor-β superfamily that is expressed in various mammalian tissues and has multiple cytokine functions, including regulating wound repair, cell differentiation, apoptosis, and embryogenesis (Risbridger et al., 2001). Moreover, activin A may induce insulin secretion in cultured human pancreatic islet cells (Florio et al., 2000), rat pancreatic islets (Totsuka et al., 1988), and enhance insulin sensitivity in hepatocytes (Ungerleider et al., 2013). Serum activin A has also been associated with acute and chronic inflammation (Phillips et al., 2009). Accruing evidence supports associations between serum activin A and cardiovascular disorders, such as acute coronary syndrome (Smith et al., 2004) and myocardial infarction (Smith et al., 2004; Ueland et al., 2012; Anastasilakis et al., 2017; Andersen et al., 2011; Miyoshi et al., 2009). Serum Activin A also predicts cardiovascular events and mortality among patients with type 2 diabetes (Ofstad et al., 2013). Associations between serum activin A, systolic blood pressure and pulse pressure among older adults were reported recently (Tsai et al., 2018).

Based on available evidence, we hypothesize that serum activin A levels may be a proxy for overall cardiometabolic risk in older individuals, after activin A secretion from reproductive organs diminishes. Our primary study objective was to use a well-established cohort of older adults to investigate the relationship between serum activin A levels and overall cardiometabolic risk, having adjusted for various potential confounding factors.

2. Methods

2.1. Study design and participants

Participants were selected from a random subsample of the I-Lan Longitudinal Ageing Study (ILAS), which is a research cohort of 1839 community-dwelling adults aged 53–92 years, who reside in I-Lan (Yilan) County, Taiwan (Hwang et al., 2015; Lee et al., 2013). Exclusion criteria were: 1) unable to communicate or cooperate with study researchers; 2) unwilling or unable to sign informed consent; 3) currently institutionalized in a long-term care facility; 4) significant functional dependence or life-expectancy of < 6 months; 5) active diseases; and 6) no longer resident in Yilan County or planning to leave in the near future. The Institutional Review Boards of National Yang Ming University and Taipei Veterans General Hospital approved this study.

2.2. Demographic characteristics and body composition

Research nurses recorded participants' demographic characteristics and medical history, and performed anthropometric measurements. Alcohol consumption behavior was categorized as current drinking or non-drinking, and tobacco usage as currently smoking or non-smoking. Total fat mass and fat-free lean body mass were calculated from whole-body dual-energy X-ray absorptiometry. Appendicular skeletal muscle mass (ASM) was defined as the total fat-free lean body mass from four limbs; the relative appendicular skeletal muscle mass index (RASM) was derived from ASM, divided by height squared (kg/m^2). Total body fat percentage was calculated as total fat mass divided by total body mass. A trained technician performed Doppler ultrasound to measure carotid intima media thickness.

2.3. Biochemistry

Peripheral blood samples were taken from all participants at 7–9 AM, after a 10-hour overnight fast. Serum biochemistry included: albumin, alanine aminotransferase, uric acid, total cholesterol, triglyceride, high-density lipoprotein (HDL) cholesterol, blood glucose, creatinine, high-sensitivity C-reactive protein (hs-CRP), insulin-like growth factor-1 (IGF-1), testosterone, and dehydroepiandrosterone sulphate (DHEA-S). The homeostasis model assessment was used to estimate insulin resistance. Estimated glomerular filtration rate (eGFR) was calculated using the Cockcroft-Gault equation. Microalbuminuria was defined urine albumin ranging from 30 mg to 300 mg. Free androgen index was calculated by dividing the total testosterone level by the sex hormone binding globulin level, then multiplying by 100.

Metabolic syndrome was defined as having three or more of the following: 1) abdominal obesity: waist circumference ≥ 90 cm in men or ≥ 80 cm in women; 2) hypertriglyceridemia: ≥ 150 mg/dl; 3) low HDL cholesterol: < 40 mg/dl in men or < 50 mg/dl in women; 4) high blood pressure: ≥ 130/85 mmHg; and 5) high fasting hyperglycemia: ≥ 100 mg/dl.

2.3.1. Activin A

Serum activin A was quantified using sandwich enzyme immunoassay (R&D systems, Inc., Minneapolis, USA);intra-assay coefficient of variation (CV) 4.2–4.4%, inter-assay CV 4.7–7.9%, mean minimum detectable dose(MDD) 3.67 pg/ml. To evaluate independent associations between activin A and other variables, serum activin A levels were stratified into low, medium and high tertiles.

2.4. Functional assessments

Functional assessments included physical, cognitive, mood, and other domains. Nutritional status was evaluated by Mini Nutritional Assessment (Guigoz, 2006). Mini-Mental State Examination score < 24 defined cognitive impairment (Folstein et al., 1975). Mood status was evaluated by the five-item geriatric depression scale (GDS-5), with GDS-5 ≥ 2 constituting depressive symptoms (Hoyl et al., 1999). Physical activity was calculated using the Chinese version of International Physical Activity Questionnaire (Qu and Li, 2004). Underlying multimorbidity was expressed according to the Charlson Comorbidity Index score (Charlson et al., 1987). Frailty status and score (sum of frailty components) were determined using the Fried criteria (Fried et al., 2001). A digital dynamometer (Smedlay's Dynamo Meter; TTM, Tokyo, Japan) was used to measure handgrip strength of the dominant hand, with the participant seated. Usual gait speed was measured by a timed 6-meter walk.

2.5. Statistical analysis

Categorical variables were expressed by percentages, and continuous data as means plus/minus standard deviations. Chi-square tests were used to compare categorical variables, and Student's *t*-test to compare continuous variables, as appropriate. Multivariate logistic regression was used to determine independent risk factors of different activin A tertiles by entering all variables with $P < 0.1$ in univariate analysis as covariates except the components of metabolic syndromes (waist circumference, serum triglyceride and HDL cholesterol, blood pressure, and serum fasting glucose) to reduce individual influence. All statistical analyses were performed using SPSS Statistics Version 18.0 for Microsoft Windows 7 (SPSS Inc., Chicago, IL, USA). A two-tailed P-value of < 0.05 was considered statistically significant.