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ORIGINAL ARTICLE

Extracellular Matrix Biomarker, Fibulin-1 and Its Association with Soluble uPAR in a Bi-ethnic South African Population: The SAfrEIC Study

Christine S. du Plooy, MSc [a], Ruan Kruger, PhD [a], Hugo W. Huisman, PhD [a*], Lars M. Rasmussen, PhD [b], Jesper Eugen-Olsen, PhD [c], Aletta E. Schutte, PhD [a]

[a]Hypertension in Africa Research Team (HART), North-West University, Potchefstroom, South Africa
[b]Centre for Individualized Medicine (CIMA); Department of Clinical Biochemistry and Pharmacology, Odense University Hospital, Denmark
[c]Clinical Research Centre 136, Copenhagen University, Hvidovre Hospital, Hvidovre, Denmark

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Background Fibulin-1 and soluble urokinase-type plasminogen activator receptor (suPAR) emerged as mediators in the development of sclerotic disease. SuPAR along with C-reactive protein (CRP) and albumin delineate inflammatory processes associated with extracellular matrix turnover in atherosclerosis. We explored the independent relationship of fibulin-1 with these inflammatory markers in a bi-ethnic South African population.

Methods This study included 290 Africans (men: n = 130 and women: n = 160) and 343 sex- and age-matched Caucasians (men: n = 160 and women: n = 183). Serum fibulin-1, suPAR, CRP and albumin levels were measured along with conventional cardiovascular and metabolic variables.

Results In both single and age-adjusted regression analyses, fibulin-1 correlated with both suPAR and albumin in African men and with suPAR in Caucasian men. These findings were absent in women. In multivariate regression analysis, these associations were confirmed in African men (R^2 = 0.22; β=0.329; p < 0.001) and Caucasian men (R^2 = 0.14; β=0.234; p = 0.008). Fibulin-1 independently associated positively with suPAR in all men, but inversely with albumin in African men only.

Conclusions These results are indicating the presence of potential subclinical inflammation (suPAR) within the extracellular matrix of endothelial tissue, contributing to the potential onset of cardiac fibrosis or vascular sclerosis among these South African men with lower albumin levels.

Keywords African • Cardiac fibrosis • Caucasian • Fibulin-1 • Inflammation • Soluble Urokinase-Type Plasminogen Activator Receptor.

Introduction

The cardiovascular extracellular matrix (ECM) scaffold undergoes continuous progressive and regressive changes; however, these changes differ between normal and pathological conditions. In pathological conditions such as hypertension, coronary artery disease and aortic stenosis, alterations in the ECM largely contribute to sclerotic processes [1]. Sclerotic progression includes the hardening, thickening or loss of resilience within connective tissue of

*Corresponding author at: Hypertension in Africa Research Team (HART), North-West University (Potchefstroom Campus), Private bag x6001, Potchefstroom, 2520, South Africa Tel.: +27 18 299 2439; fax: +27 18 285 2432, Email: hugo.huisman@nwu.ac.za

organs such as the myocardium or the lining (intima-media) of blood vessel walls [2]. In disease states such as hypertension, hyperlipidaemia or low-grade inflammation, multiple changes may occur over time and ultimately escalate into the development of atherosclerotic plaque and sclerotic lesions [3,4]. Two biomarkers, fibulin-1 [5] and soluble urokinase-type plasminogen activator receptor (suPAR), [6,7] have emerged as potential mediators in the development and progression of fibrotic and sclerotic processes.

Fibulin-1 is a fibrinogen binding glycoprotein and is expressed in the cardiac septa, cardiac valves, the skin and blood vessel walls [5–10]. A few studies have partially explored the role of fibulin-1 in the cardiovascular system [8–11]. The most conspicuous functions of fibulin-1 include cell adhesion, cell migration within the ECM and the organisation of ECM architecture in especially the basement membrane of the vasculature [12]. Fibulin-1 may reflect vascular dysfunction and fibrosis in the myocardium as a result of inflammation, by means of changes in the ECM [8,13,14].

Inflammatory mediators (such as CRP, as well as the anti-inflammatory defence system consisting of endogenous antioxidants (such as albumin)) are implicated in inflammatory processes involved in endothelial dysfunction and the development of atherosclerosis [15,16]. SuPAR, a subclinical marker of endothelial dysfunction and inflammation-related atherosclerosis, is the soluble form of the urokinase-type plasminogen activator receptor (uPAR), a glycoprotein, released from inflammatory cells [6,7]. Fibulin-1 and suPAR function via different pathways, but are potentially connected in ECM remodelling related to arterial stiffness and cardiac fibrosis.

In South Africa, a few studies have found that Africans are subjected to early changes within the vasculature such as stiffening and thickening of the blood vessel walls [11,17–19]. These studies also indicated that Africans are at higher risk for developing early cardiovascular disease due to lifestyle, an increased low-grade inflammatory profile and intrinsic risk factors [17–21]. Our study aims to compare the levels of fibulin-1, suPAR, CRP and albumin in African and Caucasian men and women. Also, in order to understand the potential functions of these markers, we further aim to explore fibulin-1 and its potential independent association with suPAR, CRP and albumin.

Materials and Methods

Study Population

The cross-sectional SAfrEIC study (**S**outh **Afr**ican study regarding the role of Sex, Age and **E**thnicity on **I**nsulin sensitivity and **C**ardiovascular function) included an initial total of 756 African and Caucasian men and women from the North West Province in South Africa. HIV-infected participants (n = 115) as well those with missing data (n = 8) were excluded from this study. A total of 290 Africans (men: n = 130; women: n = 160) and 343 Caucasians (men: n = 160; women: n = 183) were included in this study.

Study Protocol

Daily, 10 to 20 participants visited the Metabolic Unit facility at the North-West University on the Potchefstroom Campus. During the morning the participants completed a Basic Health and Demographic Questionnaire. In the event that abnormalities were identified after screening procedures, they were referred to their local clinic, hospital or physician. The protocol was approved by the Ethics Committee of the North-West University, Potchefstroom Campus and all subjects gave their written consent prior to participation (06M01 on 13 April 2007). For the investigation of human subjects, the study protocol conforms to the ethical guidelines of the Declaration of Helsinki (as revised in 2008). All participants are assured of complete anonymity where all personal information and data will be treated confidentially and also be attached to a numeric value so that outsiders cannot trace the information. Data was stored on external hard disks and DVD-ROM discs, recorded in Excel spreadsheet and is protected by a password for security of the data.

Cardiovascular Measurements

The Omron HEM-757 (Omron Healthcare, Kyoto, Japan) apparatus was used to determine systolic (SBP) and diastolic blood pressure (DBP) with the cuff on the left upper arm, whilst being in the sitting position. Each participant rested for 10 minutes prior to the blood pressure measurements after which recordings were done in duplicate at five minute intervals. The Finometer device (FMS, Finapres Medical Systems, Amsterdam, Netherlands) was used to determine total peripheral resistance and Windkessel arterial compliance. The Finometer was connected to the left arm and left index finger of the participant and measurements were recorded continuously for at least seven minutes [22]. The means of the cardiovascular variables of the last two minutes of the recordings were used for analyses.

Anthropometric Measurements

The body height, body mass and waist circumference of each participant were measured in triplicate according to standard procedures. The body height was measured to the nearest 1.0 cm using the Invicta stadiometer (Invicta Plastics 1465, Leicester, U.K) and body mass to the nearest 0.1 kg (Precision Health Scale, A & D Company, Japan). The waist circumference was measured with a Holtain non-stretchable metal flexible measuring tape. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared and rounded to 1 decimal point.

Blood Sampling and Biochemical Analyses

All participants were requested to fast for at least eight hours. A registered nurse acquired a fasting blood sample from the ante-brachial vein using a winged infusion set and measured the blood glucose level at the Metabolic Unit using enzymatic