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Bioavailable IGF-1 is beneficially associated with biomarkers of endothelial function in young healthy adults: The African-PREDICT study

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ABSTRACT

Introduction: Low circulating levels of insulin-like growth factor-1 (IGF-1) are associated with endothelial dysfunction, subsequently leading to the development of cardiovascular disease.
Objective: To better understand the early phases of vascular deterioration in a young, healthy population, we investigated, cross-sectionally, whether biomarkers of endothelial function (intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) and von Willebrand factor antigen (vWF_{ag})) are associated with IGF-1 in a healthy study population forming part of the larger African Prospective study on the Early Detection and Identification of Cardiovascular diseases and Hypertension (African-PREDICT).
Method: We included 825 black and white men and women (aged 20–30 years) and determined IGF-1, IGF binding protein-3 (IGFBP-3), ICAM-1, VCAM-1 and vWF_{ag} from blood samples. We also measured 24-h blood pressure and health behaviours namely waist circumference, accelerometery, cotinine and gamma glutamyl transferase. We used the IGF-1/IGFBP-3 M ratio as an estimate of bioavailable IGF-1.
Results: In multivariable-adjusted regression analyses performed in the total group, VCAM-1 associated positively with IGFBP-3 ($\beta = 0.21$; $p < .001$) and negatively with IGF-1/IGFBP-3 ($\beta = -0.18$; $p < .001$). ICAM-1 showed a borderline negative association with IGF-1 ($\beta = -0.09$; $p = .054$) and IGF-1/IGFBP-3 ($\beta = -0.08$; $p = .057$). vWF_{ag} was not associated with IGF-1, IGFBP-3 or bioavailable IGF-1.
Conclusion: VCAM-1 is beneficially associated with IGF-1 in a young healthy cohort, independent of sex, ethnicity, blood pressure and health behaviours – thereby confirming the potential importance of bioavailable IGF-1 in early vascular endothelial protection.

1. Introduction

Endothelial dysfunction and inflammation are considered key pathways leading to the development of atherosclerosis and subsequent cardiovascular disease [1, 2]. Increasing evidence exists regarding the endothelial-protective functions of insulin-like growth factor-1 (IGF-1), where low circulating IGF-1 have been linked to endothelial dysfunction [3], as well as cardiovascular disease and mortality [1, 4]. The crucial role of IGF-1 in counteracting endothelial dysfunction seems to be explained in part by its anti-apoptotic [5] and anti-inflammatory properties [6, 7]. IGF-1 production is stimulated by growth hormone (GH) and the beneficial effects of the GH/IGF-1 axis on vascular tone and blood pressure seems to be related to increased mRNA levels of the vascular smooth muscle ATP-sensitive potassium channel [1, 8]. In addition, IGF-1 interacts with high-affinity endothelial binding sites to increase nitric oxide production [9], and therefore has the ability to induce vasodilation [10–12], preserve coronary flow reserve [10, 11] and protect the endothelium against platelet aggregation [13, 14].

IGF-1 forms part of a complex and dynamic system involving at least six IGF-1 binding proteins (IGFBP-1 to IGFBP-6) that control the binding of IGF-1 to cell surface receptors [15]. These IGFBPs not only regulate the movement of IGF-1 between intravascular and extravascular compartments, but also regulate its availability, action and half-life [1, 16]. The most abundant IGFBP in the circulation is IGFBP-3 and approximately 80% of total IGF-1 is bound to IGFBP-3 [1, 17, 18]. Therefore, the calculation of the IGF-1/IGFBP-3 M ratio allows for an

Abbreviations: ABPM, ambulatory blood pressure monitoring; African-PREDICT, African Prospective study on the Early Detection and Identification of Cardiovascular disease and Hypertension; BMI, body mass index; IGF-1, insulin-like growth factor-1; IGFBP-3, IGF binding protein-3; ICAM-1, intercellular adhesion molecule-1; SES, socioeconomic status; VCAM-1, vascular cell adhesion molecule-1; vWF_{ag}, von Willebrand factor antigen

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estimation of bioavailable IGF-1 (IGF available for interaction with the IGF receptor) [18].

Increased levels of von Willebrand factor (vWF) are associated with endothelial dysfunction and vWF is often used for its ability to predict the prevalence or incidence of cardiovascular diseases such as myocardial infarction, stroke, fatal and non-fatal thromboembolism [19]. It is a blood glycoprotein that is synthesised by and stored in the endothelial cells. It is released from endothelial cells upon endothelial injury or damage [19–21] and therefore is indicative of endothelial functioning. In addition, intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) are expressed on cell surfaces and are also found in soluble form in plasma [22]. Clinical studies have found ICAM-1 and VCAM-1 to be related to the extent of carotid atherosclerosis [23–26], indicating a potential contribution of these adhesion molecules to the development of cardiovascular disease. Measurements of these circulating biomarkers can provide valuable insight on possible mechanisms involved and on the severity of endothelial dysfunction [27]. However, studies investigating the associations between biomarkers of endothelial function and the IGF system are limited. Available literature mostly involves elderly and diseased population groups, such as participants presenting with ischemic heart disease and acute coronary syndromes [15, 28–31]. Therefore, to better understand the early development of cardiovascular disease, we determined whether biomarkers of endothelial function (i.e. ICAM-1, VCAM-1 and vWF) are related to IGF-1 bioavailability (IGF-1, IGFBP-3 or the IGF-1/IGFBP-3 M ratio) in a young, healthy population.

2. Methods

2.1. Study population

This study forms part of the larger African Prospective study on the Early Detection and Identification of Cardiovascular diseases and Hypertension (African-PREDICT). The African–PREDICT study is an ongoing prospective study in South Africa that recruited black and white apparently healthy young adults between the ages of 20–30 years. For the purpose of this study, data from the first consecutive 825 participants with complete datasets were cross-sectionally analysed (men N = 339; women N = 486). Participants were included provided they were healthy, as defined by: (a) a brachial blood pressure of < 140 and 90 mmHg; (b) HIV uninfected; and (c) no previous diagnosis or medication use for chronic disease. We also excluded pregnant and breastfeeding women. Volunteers were recruited from Potchefstroom and surrounding areas in South Africa. Trained field workers recruited participants via their workplace, advertisements local newspapers or radio advertisements.

Approval for the African-PREDICT study was obtained from the Health Research Ethics Committee of the North-West University and adhered to the principles of the Declaration of Helsinki. All participants provided written informed consent after the procedures of the study were thoroughly explained to them. Data were collected and managed using the REDCap (Research Electronic Data Capture) electronic data capture tools hosted at the North-West University [32].

2.2. Questionnaires

Participants completed a general demographic and health questionnaire with the help of trained researchers from which the data concerning the age, sex, ethnicity and socioeconomic status (SES) of the participants were obtained. The SES was derived from three categories (skills level, education and household income). Points were given for each of these categories and the total number of points were used to determine whether a participant had a low, middle or high SES [33].

2.3. Anthropometric measurements and physical activity

Height and weight measurements were performed by following standard guidelines as described by the International Society for the Advancement of Kinanthropmetry [34]. Height (m) was measured using the SECA 213 Portable Stadiometer (SECA, Hamburg, Germany) and weight (kg), using the SECA 813 Electronic Scale (SECA, Hamburg, Germany). Waist circumference was measured with measurements taken to the nearest 0.1 cm using a non-stretchable standard tape (Lufkin, Cooper Tools, Apex North Coarolina, US). BMI was calculated as weight (kg)/height (m^2). Participants were also fitted with an ActiHeart physical activity monitor (CamNtech Ltd., England, UK) to measure activity energy expenditure. The ActiHeart device was worn for a maximum of 7 days.

2.4. Blood pressure measurements

We used the CardioXplore CE120 24-hour ambulatory blood pressure monitor (ABPM) device (Meditech, Budapest, Hungary) to collect blood pressure measurements every 30 min during the day (6:00–22:00) and every hour during the night (22:00–06:00). The ABPM was fitted to the participant's non-dominant arm with an appropriate sized cuff and participants were given instructions on how to ensure successful inflations across the 24 h time period. The study population had a mean inflation rate of 87%. Participant also filled out an ambulatory diary card during the measurements. Blood pressure data was downloaded into a database using the CardioVisions 1.9.0 Personal Edition software (Meditech, Budapest, Hungary).

2.5. Blood sampling and biochemical analyses

A registered nurse obtained fasted blood samples prior to 10 am, which were immediately taken to the on-site laboratory, centrifuged, aliquoted and stored at −80 degrees Celsius until analyses. Total serum IGF-1 and serum IGFBP-3 were determined with immunoradiometric assays (IRMA) from Immunotech (Beckman and Coulter®, Germany; IGF-1A15729; IGFBP-3 – DSL-6600). The IGF-1/IGFB-3M ratio was calculated based on 1 ng/ml IGF-1 = 0.130 nM IGF-1 and 1 ng/ml IGFBp-3 = 0.036 nM IGFBP-3 [35]. Citrate plasma samples were used to determine vWF_{ag} levels with an enzyme-linked immunosorbent assay (ELISA) (DAKO, Glostrup, Denmark). Serum samples of ICAM-1 and VCAM-1 were determined with high sensitivity Quantikine ELISA kits (R&D systems, Minneapolis, MN, USA). Polyclonal rabbit anti-vWF antibody and rabbit anti-vWF-horseradish peroxidase antibody (DAKO, Glostrup, Denmark) were used to perform the assay. The 6th International Standard for vWF/FVII was used to create the standard curve against which the samples were measured. Sodium fluoride plasma samples were used to determine glucose and serum samples were used to determine triglycerides, gamma-glutamyl transferase, high-sensitivity C-reactive protein and albumin (Cobas Integra 400plus, Roche, Basel Switzerland). A Quantikine high-sensitivity enzyme-linked immunosorbent assay from R&D Systems (R&D Systems, Minneapolis MN) was used to determine Interleukin-6 from serum. Serum cotinine was determined using a chemiluminescence method on the Immulite (Siemens, Erlangen, Germany). The intra and interassay variability for all measurements was < 10%.

2.6. Statistical analyses

The data were analysed with the computer software package Statistica version 13.0 (Dell Inc., Tulsa, Oklahoma, USA). Histograms and the Shapiro-Wilk W test were used to test for normality. Variables that were not normally distributed were logarithmically transformed (24-hour systolic and diastolic blood pressure, IGF-1, IGFBP-3, IGF-1/IGFBP-3, ICAM-1, VCAM-1, vWF_{ag}, glucose, triglycerides, C-reactive protein, cotinine and gamma-glutamyl transferase). A p-value of 0.05 or