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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

Table 1
Baseline characteristics of the African-PREDICT study population.

	Total group (n = 825)
Age (years)	24.8 ± 3.04
Anthropometric measurements	
BMI (kg/m^2)	25.4 ± 5.86
Waist circumference (cm)	80.2 ± 13.2
Blood pressure measurements	
24-hour systolic (mm Hg)	116 (105; 129)
24-hour diastolic (mm Hg)	69.0 (62.0; 76.0)
Biochemical measures	
IGF-1 (ng/ml)	234 (143; 358)
IGFBP-3 (ng/ml)	3618 (2730; 4639)
IGF-1/IGFBP-3 (molar ratio)	0.24 (0.15; 0.35)
ICAM-1 (ng/ml)	178 (82.4; 278)
VCAM-1 (ng/ml)	652 (443; 906)
vWF$_{ag}$ (%)	81.0 (44.0; 155)
Glucose (mmol/l)	4.81 (3.50; 5.45)
Triglycerides (mmol/l)	0.79 (0.47; 1.53)
Albumin (g/l)	44.8 ± 5.33
C-reactive protein (mg/l)	1.06 (0.18; 6.58)
Interleukin-6 (pg/ml)	0.97 (0.44; 2.55)
Lifestyle	
Gamma-glutamyl transferase (U/l)	20.7 (10.3; 49.2)
Cotinine (ng/ml)	1.00 (1.00; 245)
Activity energy expenditure (kCal/day)	421 ± 216

Data are arithmetic mean ± SD or geometric mean (5th and 95th percentile intervals) for logarithmically transformed variables; n, number of participants; bold text denotes statistical significance ($p < 0.05$); BMI, body mass index; ICAM-1, intercellular adhesion molecule-1; IGF-1, insulin-like growth factor-1; IGFBP-3, IGF binding protein-3; VCAM-1, vascular cell adhesion molecule-1; vWF$_{ag}$, von Willebrand factor antigen.
Bold text denotes statistical significance ($p < 0.05$).

less was regarded as statistically significant. We tested for the interaction of sex or ethnicity on the associations of vWF$_{ag}$, ICAM-1 and VCAM-1 with IGF-1, IGFBP-3 and IGF-1/IGFBP-3 by introducing appropriate interaction terms in multiple regression analyses. Pearson and partial correlations were used to determine the correlations of ICAM-1, VCAM-1 and vWF$_{ag}$ with IGF-1, IGFBP-3, and IGF-1/IGFBP-3, while adjusting for age, sex, and ethnicity in partial correlations. Additionally, vWF$_{ag}$ was adjusted for the differences in ABO blood groups of the study population. Multiple linear regression analyses were used to determine the relationship of ICAM-1, VCAM-1 or vWF$_{ag}$ with IGF-1, IGFBP-3, and IGF-1/IGFB-3. Single, partial and multiple linear regression analyses were performed in the total group, since interaction terms indicated no interaction of sex or ethnicity on any of the relationships tested (Table S1).

3. Results

The descriptive characteristics of the study participants (N = 825) are shown in Table 1. The population had a mean age of 24.8 ± 3.04 years. Mean anthropometric (BMI 25.4 ± 5.86 kg/^{2}), blood pressure (116/69 mmHg), biochemical and lifestyle measurements of the group were all within normal ranges.

We performed unadjusted and adjusted correlations between markers of endothelial activation and function (ICAM-1, VCAM-1 and vWF$_{ag}$) and markers of IGF-1 bioavailability (IGF-1, IGFBP-3 and IGF-1/IGFBP-3) (Table 2) in the total group. We plotted the main findings of single regression analyses (Fig. 1). In single and partial regressions we found that ICAM-1 was negatively associated with IGF-1 ($r = -0.11$; $p = 0.003$) and IGF-1/IGFBP-3 ($r = -0.17$; $p < 0.001$), while VCAM-1 associated positively with IGFBP-3 ($r = 0.20$; $p < 0.001$) and negatively with IGF-1/IGFBP-3 ($r = -0.13$; $p < 0.001$). No significant correlation between vWF$_{ag}$ and IGF-1 markers was evident.

In multivariable-adjusted regression analyses in the total group (Table 3), partial correlations were confirmed where ICAM-1 showed a borderline negative association with IGF-1 ($\beta = -0.09$; $p = 0.054$) and IGF-1/IGFBP-3 ($\beta = -0.08$; $p = 0.057$), while VCAM-1 associated positively with IGFBP-3 ($\beta = 0.12$; $p < 0.001$) and negatively with IGF-1/IGFBP-3 ($\beta = -0.18$; $p < 0.001$). Again, vWF$_{ag}$ showed no significant association with any of the IGF-1 markers (IGF-1: $\beta = -0.05$; $p = 0.49$; IGFBP-3: $\beta = -0.13$; $p = 0.063$; IGF-1/IGFBP-3: $\beta = 0.11$; $p = 0.09$). Based on the relationships reported in the literature with IGF-1, the regression model included the following variables: age [36], sex [37], ethnicity [38], SES score [4], waist circumference [39], 24-hour systolic blood pressure measurement [40], glucose [41], triglycerides [15], C-reactive protein [42], cotinine [43, 44], gamma-glutamyl transferase [38] and active energy expenditure [44–46].

4. Discussion

Given the protective effect of IGF-1 on endothelial function, we investigated whether biomarkers of endothelial function are related to markers of IGF-1 bioavailability (IGF-1, IGFBP-3 or IGF-1/IGFBP-3M ratio) in young adults. Notwithstanding the young healthy nature of our population, our results showed bioavailable IGF-1, as measured by IGF-1/IGFBP-3M ratio, to be beneficially associated with VCAM-1 – a robust biomarker of endothelial activation. Furthermore, bioavailable IGF-1 tended to be inversely linked to ICAM-1, another marker of endothelial activation, though the association was weaker than for VCAM-1.

The main finding of our study reflects the association between IGF-1 and markers of endothelial activation by means of cellular adhesion molecules. We found a beneficial association between bioavailable IGF-1 and VCAM-1, however, not with ICAM-1. These differences in findings could possibly be explained by the dominant role of VCAM-1, but not ICAM-1, in early atherosclerosis [47]. Earlier reports on studies

Table 2
Single and partial regression analyses showing associations of ICAM-1, VCAM-1 and vWF$_{ag}$ with IGF-1, IGFBP-3, and IGF-1/IGFBP-3.

	Total group (n = 825)					
	ICAM-1 ng/ml		VCAM-1 ng/ml		vWF$_{ag}$ %	
	r (p-value)	partial r (p-value)	r (p-value)	partial r (p-value)[a]	r (p-value)	partial r (p-value)[a,b]
IGF-1	**−0.11 (0.003)**	**−0.11 (0.003)**	−0.01 (0.64)	−0.06 (0.09)	−0.04 (0.22)	−0.01 (0.79)
IGFBP-3	**0.10 (0.006)**	0.01 (0.96)	**0.20 (< 0.001)**	**0.16 (< 0.001)**	−0.02 (0.57)	−0.01 (0.10)
IGF-1/IGFBP-3	**−0.17 (< 0.001)**	**−0.11 (0.002)**	**−0.13 (< 0.001)**	**−0.16 (< 0.001)**	−0.03 (0.33)	−0.01 (0.75)

ICAM-1, intercellular adhesion molecule-1; IGF-1, insulin-like growth factor-1; IGFBP-3, IGF binding protein-3; VCAM-1, vascular cell adhesion molecule-1; vWF$_{ag}$, von Willebrand factor antigen.
Bold text denotes statistical significance ($p < .05$).
[a] Partial correlations adjusted for age, sex and ethnicity.
[b] Additionally adjusted for differences in ABO blood groups.

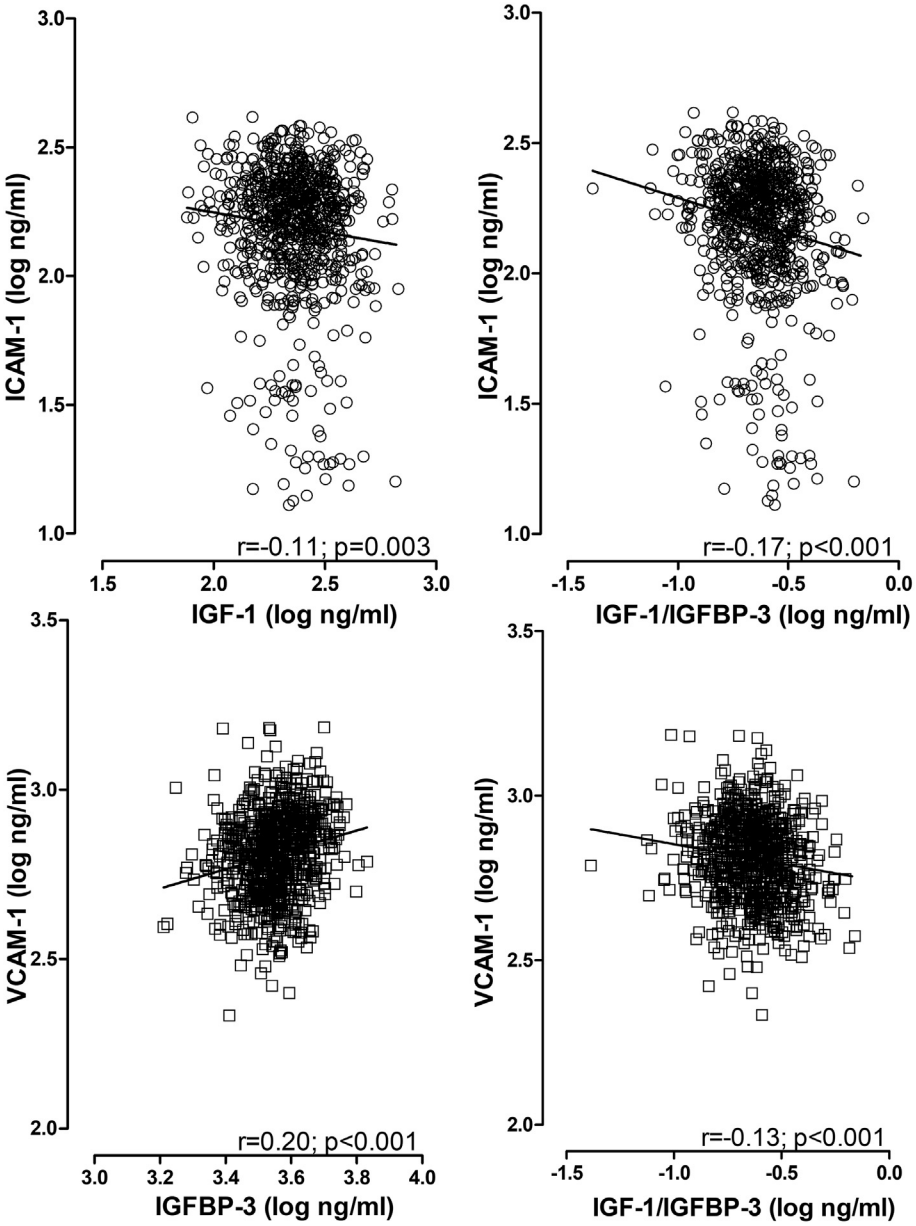

Fig. 1. Scatterplot of single regression analyses for the total groups (n = 825): ICAM-1 plotted against IGF-1, ICAM-1 plotted against IGF-1/IGFBP-3, VCAM-1 plotted against IGFBP3 and VCAM-1 plotted against IGF-1/IGFBP-3.
IGF-1, insulin-like growth factor-1; IGFBP-3, IGF binding protein-3; ICAM-1, intercellular adhesion molecule-1; VCAM-1, vascular cell adhesion molecule-1.

performed in human vascular disease specimens, showed that IGF-1 increases the expression of ICAM-1 and VCAM-1 [48]. In our healthy population we showed an opposite finding, namely inverse associations between measures of endothelial activation and IGF-1, where VCAM-1 and ICAM-1 related bioavailable IGF-1. Possible discrepancies between our findings and others could be related to the difference in the disease state of the study populations. We have previously reported in a review paper on significant negative associations between IGF-1 and blood pressure in populations with low IGF-1, and found weaker associations in populations with midrange IGF-1 concentrations (190–240 ng/ml) [49]. Therefore, our finding of linear or lack of associations in a young population with normal IGF-1 concentrations could probably be supported by a J or U-shaped relationship between VCAM-1, ICAM-1, vWF and IGF-1, as have been reported between IGF-1 and hypertension [49], cardiovascular mortality [50] and insulin resistance [51]. Another possible explanation for the negative relationship between the adhesion molecules and IGF-1 could also be due to the anti-inflammatory role of IGF-1. As possibly substantiated by in vitro data using isolated human retinal endothelial cells, IGF-1 was identified to protect against high glucose induced apoptosis and therefore important for endothelial cell survival [5].

Increased plasma vWF is closely associated with endothelial cell injury [52] and at the site of vascular injury, vWF is known to not only play an important role in platelet aggregation and adhesion, but also act as a carrier protein and protector of factor VIII [53]. Accordingly, previous results in an older study population indicated a beneficial association between vWF and bioavailable IGF-1 [54]. Therefore, highlighting the importance of IGF-1 in conserving endothelial function [20, 21]. However, in our young healthy population we found no association between vWF and any of the markers of endothelial protection. This may reflect the specific eligibility criteria of the African-PREDICT study, where individuals with hypertension or chronic disease were excluded, and thus did not yet present with endothelial injury.

It is known that IGF-1 levels decrease with increasing age

Table 3
Multiple regression analyses with vWF_{ag}, ICAM-1 and VCAM-1, respectively, as dependent variables and IGF-1, IGFBP-3, and IGF-1/IGF-3, respectively, as main independent variables.

	Total group (n = 825)		
	ICAM-1 (ng/ml)	VCAM-1 (ng/ml)	vWF_{ag} (%)[a]
IGF-1	$R^2 = 0.13$	$R^2 = 0.09$	$R^2 = 0.04$
	β = −0.09	β = −0.06	β = −0.05
	p = 0.054	p = 0.16	p = 0.49
IGFBP-3	$R^2 = 0.13$	**$R^2 = 0.12$**	$R^2 = 0.05$
	β = −0.01	**β = 0.21**	β = −0.13
	p = 0.96	**p < 0.001**	p = 0.063
IGF-1/IGFBP-3	$R^2 = 0.13$	**$R^2 = 0.11$**	$R^2 = 0.05$
	β = −0.08	**β = −0.18**	β = 0.11
	p = 0.057	**p < 0.001**	p = 0.09

ICAM-1, intercellular adhesion molecule-1; IGF-1, insulin-like growth factor-1; IGFBP-3, IGF binding protein-3; VCAM-1, vascular cell adhesion molecule-1; vWF_{ag}, von Willebrand factor antigen.
Other variables included in the model: age; ethnicity; sex; SES; waist circumference; 24-h systolic blood pressure measurement; glucose; triglycerides; C-reactive protein; interleukin-6; cotinine; gamma-glutamyl transferase, activity energy expenditure.
Bold text denotes statistical significance ($p < 0.05$).
[a] Additionally adjusted for differences in ABO blood groups.

throughout adulthood [36]. Previous research from our group have shown an early decline in total IGF-1 at younger ages (40 years of age) in black compared to white African populations [38] and also a negative association between bioavailable IGF-1 and a number of the metabolic syndrome components [55]. Others have shown that lifestyle and behavioural factors, such as obesity [39, 56], physical inactivity [44–46], psychological distress, increased alcohol intake and smoking [43, 57], to supress bioavailability of IGF-1. Collectively, previous findings on how health behaviours affect IGF-1 levels and the findings from our study, highlight the importance of maintaining a healthy lifestyle at an early age. It is plausible that maintaining the bioavailability of IGF-1 may provide protection against endothelial dysfunction and earlier disease onset.

The findings of our study should be interpreted in light of its strengths and limitations. Due to the cross-sectional nature of our analysis, we cannot infer causality. Nevertheless, our findings form part of the baseline phase of the African-PREDICT study allowing detailed future prospective analyses in the future. The main strengths of this study are the inclusion of participants with a within a very specific age range (20–30 years) and also the availability of data regarding bioavailable IGF-1 (IGF-1/IGFBP-3M ratio) in a large group of participants who underwent measurements under highly-controlled conditions.

To conclude, we found markers of endothelial activation to be beneficially associated with IGF-1 in a young healthy cohort, thereby confirming the potential importance of bioavailable IGF-1 in early endothelial vascular protection.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ghir.2018.06.002.

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Any opinion, findings, and conclusions or recommendations expressed in this material are those of the authors, and therefore, the NRF does not accept any liability in this regard.

Author contributions

SAB was responsible for the statistical analysis, interpretation of data and writing of the draft manuscript. WS, CMCM, SB were responsible for interpretation of results and critical review of the manuscript. AES is the principal investigator of the African-PREDICT study, and was involved with conceptualising the paper, critical interpretation of results, and critical review of the manuscript.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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