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Predictors of variation in serum IGFI and IGFBP3 levels in healthy African-American and white men

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Abstract

Background—Individual variation in circulating insulin-like growth factor-I (IGF1) and its major binding protein, insulin-like growth factor binding protein-3 (IGFBP3) have been etiologically linked to several chronic diseases, including some cancers. Factors associated with variation in circulating levels of these peptide hormones remain unclear.

Methods—Multiple linear regression models were used to determine the extent to which socio-demographic characteristics, lifestyle factors, personal and family history of chronic disease, and common genetic variants, the $(CA)_n$ repeat polymorphism in the *IGF1* promoter and the *IGFBP3* -202 A/C polymorphism (*rs2854744*) predict variation in IGF1 or IGFBP3 serum levels in 33 otherwise healthy African American and 37 white males recruited from Durham Veterans Administration Medical Center.

Results—Predictors of serum IGF1, IGFBP3 and the IGF1:IGFBP3 molar ratio varied by race. In African Americans, 17% and 28% of the variation in serum IGF1 and the IGF1:IGFBP3 molar ratio, respectively, was explained by cigarette smoking and carrying the *IGF1* $(CA)_{19}$ repeat allele, respectively. Not carrying at least one *IGF1* $(CA)_{19}$ repeat allele and a high BMI explained 8%

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and 14%, respectively, of the variation IGFBP3 levels. These factors did not predict variation of these peptides in whites.

Conclusion—If successfully replicated in larger studies, these findings add to recent evidence suggesting known genetic and lifestyle chronic disease risk factors influence IGF1 and IGFBP3 circulating levels differently in African Americans and whites.

Keywords

insulin-like growth factors; predictors; race

Introduction

IGF1 is a potent broad-spectrum mitogenic growth factor with antiapoptotic properties. Elevated circulating concentrations of IGF1 have been etiologically linked to several chronic diseases, including type-2 diabetes,[1] cardiovascular diseases,[2, 3] and cancers of the breast,[4–6] colon,[7, 8] and prostate.[6, 9–18] Circulating IGF1 levels are modulated by the formation of the ternary complex that binds to IGFBP3 and/or IGFBP5 and an acid labile subunit (ALS) too large to pass through the endothelial wall.[6, 19] Independently of regulating the availability of IGF1 in circulation, IGFBP3 also induces apoptosis.20 Lower circulating concentrations of IGFBP3 have also been linked to increased risk of several malignancies.[6, 9, 11, 13, 17, 21–23]

For reasons that are still poorly understood, there is considerable inter-individual variation in serum concentrations of both IGF1 and IGFBP3. Whereas age-related declines in IGF1 and IGFBP3 serum levels have been repeatedly demonstrated in men and women,[24–27] data on the utility of demographic and lifestyle factors such as cigarette smoking, sex,[24, 26, 28, 29] race,[30–33] and body mass index (BMI), to predict variation in these peptides are inconsistent. In addition, although common nonsynonymous genetic variants in *IGF1* and *IGFBP3* have been evaluated in relation to chronic disease risk in many case-control studies because of their association with circulating protein products of these genes, the capacity of these variants to predict circulating levels also remains unclear.[27, 34–36] The availability of both genetic variant and lifestyle data in otherwise healthy African American and white men provided the impetus to evaluate the extent to which together these factors predict IGF1 and IGFBP3 serum concentrations in healthy men.

Methods

Study Participants

Participants included in these analyses served as healthy controls for a hospital-based, case-control study of prostate cancer conducted at the Durham Veterans Administration Medical Center (DVAMC). Methods of participant accrual and data collection have been detailed elsewhere.[37, 38] Briefly, as part of a hospital-based, case-control study, 181 consecutive hospital controls aged 40 to 75 years were identified and matched to cases by race and age, between January, 1999, and July, 2001, at the DVAMC, North Carolina. Of the 181 controls identified, 96 were enrolled, 2 withdrew, and 2 were lost between identification and interview, a response rate of 53%. We further excluded 26 men for whom genotype or other covariate data were unavailable such that 70 participants were available for these analyses, 33 of them African American.

Data Collection

On scheduled visits to the DVAMC, a trained nurse conducted in-person interviews using a standardized questionnaire to obtain data on socio-demographic and lifestyle factors, as well

as family and personal history of several chronic diseases, including prostate cancer, other cancers, and diabetes. Following the interview, 30mls of peripheral blood were collected in 10mls EDTA-treated tubes. Serum and buffy coat were isolated within 2hours of collection and stored in a −70°C freezer. PureGene system reagents (Gentra, Minneapolis, MN) were used to extract and re-suspend genomic DNA according to manufacturer's protocol.

Genotyping

Detailed methods for ascertaining polymorphic variants also have been previously described. To determine the repeat length of the *IGF1* $(CA)_n$ microsatellite, located 1kb upstream of the gene's transcription start site, PCR was performed using previously published unlabelled primers obtained from Integrated DNA Technologies (Coralville, Iowa). The forward and reverse primers used were 5'-GCT AGC CAG CTG GTG TTA TT-3' and 5'-ACC ACT CTG GGA GAA GGG TA-3', respectively. The *IGFBP3* single nucleotide polymorphism (-202 (A/C) (rs2854744) was analyzed according to Deal et al. [34] The forward and reverse primers used were 5'-CCA CGA GGT ACA CAC GAA TG-3' and 5'-AGC CGC AGT GCT CGC ATC TGG-3', respectively.

Serum measurement of IGF1 and IGFBP3

We measured IGF1 and IGFBP3 concentrations at the time of data collection. Measurements were according to manufacturer's protocol, in duplicate using commercially available enzyme-linked immunosorbent assay (ELISA) kits (Diagnostic Systems Laboratories, Webster, TX). Each assay batch included positive controls and masked samples derived from pooled serum specimens. If the two measurements were widely divergent (an infrequent occurrence), assays were repeated up to two additional times. The average of two measurements for each analyte was used for data analysis. The sensitivities of the assay used were as follows: IGF1=0.03ng/ml and IGFBP3=0.04ng/ml. In addition to quantifying IGF1 and IGFBP3 concentrations, we also estimated the molar ratio of IGF1/IGFBP3 as the quantity (IGF1 in ng/ml*0.130)/IGFBP3ng/ml*0.036) where the constants are the molecular weights of the respective polypeptide. The molar ratio is often used as a surrogate for the more relevant unbound IGF1. [24, 31]

Statistical analyses

Age-adjusted means and standard deviations for IGF1, IGFBP3 and the IGF1:IGFBP3 molar ratio, were computed for the overall sample and in the presence and absence of each predictor for African Americans and whites together as well as separately by race. Predictors were dichotomized as follows: age (<60 years v. older ≥60 years); education (graduated from high school v. not graduated from high school); smoking (100 cigarettes in a lifetime v. never smoked 100 cigarettes in a lifetime); diabetic v. not diabetic; normal BMI (BMI<25kg/m^2) v. overweight (BMI=25-<30kg/m^2) v. obese (BMI≥30kg/m^2); family history of prostate cancer in father or brother v. none; homozygote and heterozygote carriers v. noncarrier of the *IGF1* $(CA)_{19}$ repeat allele; homozygote and heterozygote carriers v. noncarrier of the *IGFBP3* −202bp A-allele. Multiple regression models using PROC REG in SAS (Cary, NC) were used to identify factors independently associated with IGF1 and IGFBP3 levels. Using backward selection strategies, beta coefficients and partial r^2 for each factor in the final model were also computed to determine the proportion of variation contributed by each factor. Although age did not independently predict decrease in total IGF1 or IGFBP3 concentration, it was retained in all models since it is a known determinant of these peptides. Statistical analyses were conducted using SAS version 9.3 (SAS, Cary, NC, USA).

Results

The distribution and age-adjusted means and 95% confidence intervals for serum IGF1, IGFBP3 and IGF1:IGFBP3 molar ratios of 33 African American and 37 white men are presented in Table 1. Among all participants, serum levels of IGF1, IGFBP3 and IGF1:IGFBP3 molar ratio did not vary significantly by diabetes, body mass index, family history of prostate cancer or carrying the A/C at −202bp of the *IGFBP3* genotypes. However, African-American noncarriers of the *IGF1 (CA)* $_{19}$ repeat had lower IGF1 levels (117; 95%CI=94–140ng/ml) and lower IGF1:IGFBP3 molar ratio (0.21; 95%CI=0.17–0.25) compared to whites. Also, cigarette smoking African Americans had somewhat lower IGF1:IGFBP3 molar ratio and IGF1 levels compared to white smokers (IGF1 mean=114ng/ml; 95%CI=97–130 for African Americans versus mean=131ng/ml; 95%CI=109–153 for whites; IGFBP1:IGFBP3 molar ratio 0.22 and 0.27 for African Americans and white men, respectively). African-American men with a high BMI had lower levels of IGF1 and IGF1:IGFBP3 molar ratio compared to whites.

Similar to previous reports[39, 40], in race-stratified analyses multivariable regression models fit to identify significant predictors of serum concentrations of IGF1, and IGF1/IGFBP-3 molar ratio (Table 2), we found that age, circulating IGF1 and IGFBP3 were inversely related, predicting most of the variation in serum IGF1 and IGFBP3. In contrast, no other factors were significant predictors of circulating IGF1 or IGFBP3 levels in white men. However, in African-American men, the two independent predictors of serum IGF1 levels were; a history of cigarette smoking and carrying the *IGF1 (CA)*$_{19}$ repeat allele. These two factors explained 17% of the individual variation in IGF1 and 28% of the variation in IGF1:IGFBP3 molar ratio, whereas, a large BMI and being a noncarrier of the *IGF1 (CA)*$_{19}$ repeat explained 22% of the variation in circulating IGFBP3. Factors previously reported to predict IGF1 and IGFBP3, including a high fat diet, alcohol use, diabetes, carrying the *IGFBP3* –202 C-allele, and a large waist circumference, did not independently predict serum IGF1 or IGFBP3 in African Americans or whites

Discussion

In this study, we found that the effect of lifestyle factors, including cigarette smoking and a large BMI as well as carrying at least one *IGF1 (CA)*$_{19}$ repeat allele predicted serum IGF1 and IGFBP3 in African Americans but not whites, explaining 28% of the variation in IGF1:IGFBP3 molar ratio; 17% of the variation in serum IGF1 and 22% of the variation in serum IGFBP3. These findings contrast with those of other studies where no racial differences in the effect of genetic or lifestyle factors were found. [39–41] Although IGF1 and IGFBP3 proteins have been evaluated extensively in different race/ethnic groups, to our knowledge, this is the first study to demonstrate the utility of this common genetic variant together with lifestyle factors to predict serum IGF1 and IGFBP3 in otherwise healthy African- American men, suggesting that race/ethnicity-dependent mechanisms are important. If confirmed, these findings may explain, in part, inconsistent findings among studies evaluating associations between established risk factors and chronic disease endpoints where race/ethnicity is data are not taken into account.

The finding that carrying at least one copy of the *IGF1* $(CA)_{19}$ dinucleotide repeat allele predicted IGF1 and IGFBP3 levels in African Americans, but not in whites contrasts with at least three of the five studies that have evaluated the association between carrying the *IGF1*$(CA)_{19}$ allele, and IGF1 or IGFBP3 levels[24, 31, 35, 36] where lower levels of IGF1 were found among predominantly white individuals carrying this common genetic variant. In Japanese27 and British[42] studies, no association between carrying the IGF1 $(CA)_{19}$ repeat allele and IGF1 levels was found, although increased IGFBP3 levels were noted by others.[27]

These studies had few or no African Americans. In a large American multiethnic study, no race/ethnic differences in the relationship between carrying the *IGFBP3 -202A/C* and serum IGFBP3 or IGF1 were noted.[40]

Our findings that African-American men with a history of cigarette smoking had lower IGF1 levels and a lower IGF1:IGFBP3 molar ratio are consistent with those of some previous studies,[43, 44] although not all studies have confirmed this association.[26, 29, 45, 46] The association between a higher BMI and higher IGFBP3 levels have also been reported by some[30, 42, 44] although others did not find this association.[24,47] While the mechanisms underlying racial/ethnic differential effects of common environmental stressors such as a large BMI and cigarette smoking are still under investigation, if confirmed by other studies, our findings will contribute to our understanding of chronic disease risk involving IGF-signaling in African Americans.

A limitation of the analyses was that while our sample size was adequate to assess the independent effects of the factors under investigation, it was inadequate to evaluate the interaction between genetic factors and demographic and lifestyle factors on serum IGFBP3 or IGF1. However, a larger more recently published study reported no interaction effect between the *IGFBP3 -202A/C* variant and lifestyle factors.[40] Another limitation is the low (53%) response rate, potentially raising concerns about the generalizability of findings to the general population. However, the main reason for non-response was failure to contact following identification by clinic registries; a reason unlikely to be related to serum IGFI or IGFBP3 or factors assessed in our analyses.

In summary, commonly identified risk factors for chronic diseases, including a history of cigarette smoking, a large BMI and carrying at least one *IGF1* $(CA)_{19}$ repeat allele predicted variation in serum IGF1 and IGFBP3 levels in African-American men but not white men. These findings suggest that while variations in serum IGFs are clearly regulated by endogenous complex physiologic systems, some lifestyle and genetic variants appear to operate differently depending on race/ethnicity. If confirmed in larger studies, our observations will contribute to a more detailed understanding of ethnicity/race-specific insulin-like growth factor signaling pathway which should guide public health and therapeutic interventions.

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Table 1

Age-adjusted Mean Serum IGF1, IGFBP3 and IGF1:IGFBP3 Molar Ratio among healthy African-American and white men

Characteristic	Overall (N=70)		African Americans (N=33)		whites (N=37)	
Never smoked 100 cigarettes n (%)	15	(21.4)	10	(30.3)	5	(13.5)
IGF1, Mean (95% CI)	132	(104–159)	151	(126–176)	102	(46–158)
IGFBP3, Mean (95% CI)	1799	(1393–2205)	2037	(1665–2410)	1438	(565–2311)
IGF1:IGFBP3, Mean (95% CI)	0.28	(0.24–0.32)	0.28	(0.24–0.33)	0.27	(0.19–0.36)
Ever smoked 100 cigarettes n (%)	55	(78.6)	23	(69.7)	32	(86.5)
IGF1, Mean (95% CI)	125	(110–139)	114	(97–130)	131	(109–153)
IGFBP3, Mean (95% CI)	1874	(1623–2086)	1874	(1629–2119)	1856	(1518–2195)
IGF1:IGFBP3, Mean (95% CI)	0.25	(0.24–0.29)	0.22	(0.19–0.25)	0.27	(0.24–0.30)
BMI <25 kg/m^2 n (%)	11	(15.7)	5	(15.2)	6	(16.2)
IGF1, Mean (95% CI	121	(89–153)	121	(82–159)	131	(76–187)
IGFBP3, Mean, (95% CI)	1810	1338–2282)	1837	(1370–2305)	1916	(1039–2794)
IGF1:IGFBP3, Mean, (95% CI)	0.24	(0.19–0.29)	0.23	(0.16–0.30)	0.24	(0.15–0.32)
BMI 25- <30 kg/m^2 n (%)	27	(38.6)	11	(33.3)	16	(43.2)
IGF1, Mean (95% CI)	114	(94–134)	113	(87–139)	111	(80–143)
IGFBP3, Mean (95% CI)	1627	(1332–1922)	1561	(1247–1876)	1632	(1138–2127)
IGF1:IGFBP3, Mean (95% CI)	0.27	(0.24–0.30)	0.26	(0.22–0.31)	0.28	(0.23–0.32)
BMI ≥30 kg/m^2 n (%)	32	(45.7)	17	(51.5)	15	(40.5)
IGF1, Mean (95% CI)	138	(120–157)	135	(114–156)	142	(110–174)
IGFBP3, Mean (95% CI)	2069	(1799–2340)	2183	(1931–2435)	1932	(1429–2434)
IGF1:IGFBP3, Mean (95% CI)	0.25	(0.22–0.28)	0.23	(0.19–0.27)	0.28	(0.23–0.32)
Non-carriers of the IGF1 (CA)$_{19}$ genotype, n (%)	19	(27.1)	14	(42.4)	5	(13.5)
IGF1, Mean (95% CI)	119	(95–144)	117	(94–140)	136	(79–193)
IGFBP3, Mean (95% CI)	1921	(1558–2284)	2084	(1775–2393)	1585	(711–2460)
IGF1:IGFBP3, Mean (95% CI)	0.23	(0.19–0.27)	0.21	(0.17–0.25)	0.29	(0.21–0.37)
Heterozygous for the (CA)$_{19}$ genotype, n (%)	28	(40.0)	14	(42.4)	14	(37.8)
IGF1, Mean (95% CI)	129	(109–149)	133	(110–156)	124	(90–158)
IGFBP3, Mean (95% CI)	1805	(1506–2105)	1872	(1563–2181)	1720	(1195–2244)
IGF1:IGFBP3, Mean (95% CI)	0.27	(0.24–0.30)	0.26	(0.22–0.30)	0.28	(0.23–0.33)

Characteristic	Overall (N=70)		African Americans (N=33)		whites (N=37)	
Homozygous for the $(CA)_{19}$ genotype, n (%)	23	(32.9)	5	(15.2)	18	(48.6)
IGF1, Mean (95% CI)	128	(106–151)	126	(87–165)	127	(97–157)
IGFBP3, Mean (95% CI)	1870	(1539–2202)	1619	(1102–2136)	1922	(1463–2381)
IGF1:IGFBP3, Mean (95% CI)	0.26	(0.23–0.29)	0.28	(0.22–0.35)	0.25	(0.21–0.30)
***IGFBP3* −202bp AA genotype**	16	22.9	10	30.3	6	16.2
IGF1, Mean (95% CI)	125	(99–152)	137	(110–164)	114	(58–170)
IGFBP3, Mean (95% CI)	1642	(1255–2029)	1725	(1365–2086)	1600	(744–2456)
IGF1:IGFBP3, Mean (95% CI)	0.27	(0.23–0.31)	0.29	(0.24–0.33)	0.24	(0.16–0.32)
***IGFBP3* −202bp AC genotype**	31	44.3	15	45.5	16	43.2
IGF1, Mean (95% CI)	125	(106–144)	115	(92–137)	133	(101–165)
IGFBP3, Mean (95% CI)	2062	(1785–2338)	2124	(1830–2419)	1988	(1503–2472)
IGF1:IGFBP3, Mean (95% CI)	0.23	(0.20–0.26)	0.20	(0.17–0.24)	0.26	(0.21–0.30)
***IGFBP3* −202bp CC genotype**	23	32.9	8	24.2	15	40.5
IGF1, Mean (95% CI)	129	(107–151)	130	(99–161)	126	(93–159)
IGFBP3, Mean (95% CI)	1735	(1413–2057)	1795	(1388–2203)	1679	(1174–2184)
IGF1:IGFBP3, Mean (95% CI)	0.28	(0.25–0.31)	0.26	(0.21–0.31)	0.29	(0.24–0.34)

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Table 2

Multivariable linear regression models for serum levels of IGFs by race

	African Americans			whites		
	β (SE)	**P-value (Model) Variable**	**r^2 (Model) Partial**	**β (SE)**	**P-value (Model) Variable**	**r^2 (Model) Partial**
IGF1		**(0.0005)**	**(0.50)**		**(<0.0001)**	**(0.68)**
Age at interview	−0.92 (0.65)	0.17	0.09	−1.111 (1.203)	0.36	0.07
Ever smoked 100 cigarettes (yes/no)	−29.60 (12.69)	0.03	0.15	--	ns	--
IGF1 (CA)19 repeat (carrier/non-carrier)	24.07 (12.03)	0.06	0.02	--	ns	--
IGFBP3 serum level	0.039 (0.011)	0.001	0.23	0.052 (0.007)	<0.0001	0.61
IGFBP3		**(0.0006)**	**(0.49)**		**(<0.0001)**	**(0.67)**
Age at interview	−0.524 (8.89)	0.95	0.03	−0.299 (18.78)	0.99	0.05
BMI (kg/m2)	34.45 (13.77)	0.02	0.14	--	ns	--
IGF1 (CA)19 repeat (carrier/non-carrier)	−409.1 (155.5)	0.01	0.08	--	ns	--
IGF1 serum level	6.94 (1.90)	0.001	0.24	12.49 (1.55)	<0.0001	0.62
IGF1:IGFBP3		**(0.02)**	**(0.29)**		**(0.82)**	**(0.001)**
Molar Ratio						
Age at interview	−0.001 (0.001)	0.59	0.01	0.001 (0.003)	0.82	0.001
Ever smoked 100 cigarettes (yes/no)	−0.055 (0.024)	0.03	0.13	--	ns	--
IGF1 (CA)19 repeat (carrier/non-carrier)	0.055 (0.023)	0.02	0.15	--	ns	--

ns = not significant in the model

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