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Serum Insulin-Like Growth Factor-1 Binding Proteins 1 and 2 and Mortality in Older Adults: The Health, Aging, and Body Composition Study

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Abstract

OBJECTIVE—To evaluate the relationship between serum insulin-like growth factor 1 (IGF-1), IGF-1 binding protein 1 (IGFBP-1), and IGF-1 binding protein 2 (IGFBP-2) and fasting insulin, fasting glucose, adiposity, and mortality in older adults.

DESIGN—A prospective cohort study with mean follow-up of 6.2 years.

SETTING—Participants were recruited and followed at two centers affiliated with academic medical institutions.

PARTICIPANTS—Six hundred twenty-five men and women aged 70 and older and in good health at the time of enrollment.

MEASUREMENTS—Serum IGF-1, IGFBP-1, and IGFBP-2; fasting serum insulin; fasting serum glucose; visceral fat; and total percent fat.

RESULTS—Higher IGFBP-1 and higher IGFBP-2 were significantly associated with lower fasting insulin, lower fasting glucose, and lower adiposity, but higher IGFBP-1 and IGFBP-2 were associated with greater mortality. In multivariate adjusted models, the hazard ratio for all-cause mortality was

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1.48 (95% confidence interval (CI)=1.14–1.92) per standard deviation (SD) increase in IGFBP-2 and 1.34 (95% CI = 1.01–1.76) per SD increase in IGFBP-1. No association was found between IGF-1 and all-cause mortality.

CONCLUSIONS—Higher IGFBP-1 and IGFBP-2 are associated with lower adiposity and decreased glucose tolearance but also with greater all-cause mortality. Higher levels of serum IGF-1 binding protein (IGFBP) may indicate greater IGF-1 activity and thus represent an association between higher IGF-1 activity and mortality in humans.

Keywords

aging; IGF-1; IGFBP; mortality

Insulin-like growth factor 1 (IGF-1) is an endocrine hormone, primarily synthesized in the liver. IGF-1 synthesis and secretion is mainly stimulated by growth hormone.[1] IGF-1 controls postnatal body growth, cell proliferation, and apoptosis.[2] It plays an important role in the metabolism of growth hormone, insulin, and glucose.[1] The IGF-1 signaling pathway is involved in the control of lifespan in model organisms. Mutations of genes in this pathway alter life span in model organisms as diverse as nematodes, fruit flies, and mice.[3,4] In general, mutations that decrease signaling through this pathway are associated with greater longevity.[3] For example, mice with deletion of one copy of the IGF-1 receptor show greater resistance to oxidative stress and survive approximately 26% longer than their littermate controls.[5]

IGF-1 is bound to six major different binding proteins, which modulate its activity, in some cases sequestering it and reducing IGF-1 signaling and in some cases potentiating its effects.[2] IGF-1 binding proteins (IGFBPs) prolong the half-life of IGF-1 and regulate its clearance. IGFBPs control the diffusion and efflux of IGF-1 from the vascular space and also inhibit or facilitate interaction of IGF-1 with its receptors.[6] In human epidemiological studies, lower IGF-1 binding protein 1 (IGFBP-1) and IGF-1 binding protein 2 (IGFBP-2) have been associated with grater insulin resistance, including higher fasting glucose and higher fasting insulin levels,[7–10] although paradoxically, higher levels of IGFBP-1 have been associated with greater mortality.[11] Lower levels of IGF-1 binding protein 3 (IGFBP-3) have been found to be associated with greater mortality in one study,[12] but another study has negated these results.[11] These previous findings suggest that IGFBPs might be biomarkers of aging.

To further investigate the role of IGFBPs as predictors of insulin resistance and mortality, the association between serum IGF-1 and IGFBPs (IGFBP-1 and IGFBP-2) were evaluated in the Health, Aging, and Body Composition (Health ABC) cohort. Specifically, the associations between serum IGF-1, IGFBP-1, and IGFBP-2 and fasting insulin, fasting glucose, visceral fat, and total percent fat were tested in Health ABC participants. In addition the associations between serum IGF-1, IGFBP-1, and IGFBP-2 and mortality were tested.

METHODS

Participants

Data from the Health ABC Study were used. This study was designed to investigate causes of functional changes with age. Participants included 3,075 black and white older adults (aged 70–79) recruited in and around Memphis, Tennessee, and Pittsburgh, Pennsylvania, between 1997 and 1998. At the time of enrollment, all participants were able to walk one-quarter of a mile, climb 10 steps, and perform daily activities without aid. Individuals were excluded from the study if they required assistive devices or equipment to get around, had a life-threatening illness, had a history of active treatment for cancer in the previous 3 years, were currently enrolled in a lifestyle intervention treatment, or planned to move out of the area within 3 years.

Participants were contacted every 6 months at clinic visits or in telephone interviews. Vital status, functional limitations, all hospitalizations, and selected outpatient events were ascertained. A central committee adjudicated all deaths for immediate and underlying causes of death through death certificates, hospital records, and a proxy interview. All participants provided informed written consent for participation. The institutional review boards of the clinical sites and the Data Coordinating Center at the University of California at San Francisco) approved the study protocol.

Of the total cohort, 625 randomly selected participants were included in the current analysis. Of these participants, 623 had IGF-1 measurements, 610 had IGFBP-1 measurements, and 621 had IGFBP-2 measurements. Blood samples were collected with venipuncture after an 8-hour overnight fast at the baseline visit. The specimens were processed and aliquoted into cryovials. They were then frozen at −70°C and shipped to the study laboratory storage facility.

Measurement of IGF-1, IGFBP-1, and IGFBP-2

Serum IGF-1 level was measured using radioimmunoassay (RIA) for the quantitative determination of IGF-1 (IGFBP blocked) (ALPCO Diagnostics, Windham, NH), with an interassay coefficient of variation (CV) of 7.4%. Serum IGFBP-1 was determined using the Total IGFBP-1 IRMA kit and serum IGFBP-2 was determined using the IGFBP-2 RIA kit (Diagnostic Systems Laboratories, Inc., Webster, TX). The intra - and interassay CVs are 2.7% to 4.6% and 3.5% to 6.0% for IGFBP-1 and 4.7% to 8.5% and 4.5% to 7.4% for IGFBP-2.

Measurement of Other Variables

Demographic variables (age, race, sex) were assessed according to questionnaire. The height and weight measurements included in the analyses were measured at the first study visit. Visceral fat was measured using computed tomography (CT) scans (Somatom Plus 4, Siemens, Erlangen, Germany; Picker PQ 2000S, Marconi Medical Systems, Cleveland, OH; or 9800 Advantage scanner, General Electric, Milwaukee, WI) with standardized protocols. CT scans were performed with participants in the supine position, and visceral fat was calculated at the L4–L5 level. Body composition was determined using dual-energy X-ray absorptiometry (QDR 4500, Hologic, Inc., Waltham, MA). Serum glucose level was measured using a colorimetric technique on a Vitrols 950 analyzer (Johnson & Johnson, New Brunswick, NJ) with a CV of 1.0% to 1.4%. Serum insulin was measured using RIA (Pharmacia, Uppsala, Sweden). Serum C-reactive protein (CRP) was measured using enzyme-linked immunosorbent assay (ELISA) based on purified protein and polyclonal anti-CRP antibodies (Calbiochem, EMD Biosciences Inc., Darmstadt, Germany). The CRP assay was standardized according to the World Health Organization's First International Reference Standard. The interassay CV of CRP assay was 8%. Serum interleukin 6 (IL6) was measured using solid-phase ELISA (R&D Systems, Minneapolis, MN), with a CV of 13.1% to 18.1%.

Statistical Analysis

Univariate comparisons between individuals who survived and those who did not were performed for race, sex, baseline age, body mass index (BMI), weight, height, total percent fat, visceral fat, fasting glucose, fasting insulin, CRP, IL6, IGF-1, IGFBP-1, and IGFBP-2. Categorical variables (race and sex) were compared using chi-square tests. Continuous variables that were approximately normally distributed (BMI, total percent fat, weight, height, and IGF-1) were compared using the *t*-test. Continuous variables that were not normally distributed (baseline age, visceral fat, CRP, IL6, fasting glucose, fasting insulin, IGFBP-1, and IGFBP-2) were compared using the Wilcoxon rank sum test.

The association between IGF-1, IGFBP-1, and IGFBP-2 and fasting insulin and total percent fat was estimated with linear regression using the log-transformed values of insulin and total

percent fat as outcome variables because these were normally distributed. Because fasting glucose and visceral fat were not normally distributed with or without log transformation, their associations with IGF-1, IGFBP-1, and IGFBP-2 were investigated using logistic regression. Fasting glucose and visceral fat were dichotomized using their top and bottom quartiles. Participant's sex, race, study site, and baseline age were used as covariates in the model. To avoid confounding due to treatment, 70 participants who were known to have diabetes mellitus at the time of the measurement were excluded.

Cox proportional hazards models were used to test the association between IGF-1, IGFBP-1, and IGFBP-2 and mortality. Two sets of multivariate models were tested. In the first set, baseline age, sex, study site, and race were adjusted for to confirm that there was no confounding by these demographic factors. In the second set of models, height, weight, visceral fat, total percent fat, fasting glucose, fasting insulin, serum IL6, and serum CRP were added to the demographic variables to determine whether these factors confound the associations detected in the baseline models. The proportionality assumption for the Cox analysis was checked by testing the correlation between Schoenfeld residuals and survival time.

The values of IGFBP-1, IGFBP-2, fasting insulin, IL6, and CRP were log transformed before entering them into the Cox proportional hazards models, because their original values were not normally distributed. Other variables that were not normally distributed, including visceral fat and fasting glucose, were entered into the Cox proportional hazards models using their quartiles, because neither log transformation nor other transformations converted them to a normal distribution. To compare the strength of association between variables, IGF-1, log-transformed IGFBP-1, and log-transformed IGFBP-2 were divided by their standard deviations (SDs) so that the hazard ratio was associated with a 1-SD change in the measurement. Proportional hazards assumptions were examined for both models. In the first set of models, *P*-values for the correlation between Schoenfeld residuals and survival time were .41 for IGF-1, .71 for IGFBP-1, and .26 for IGFBP-2. In the second set of models, *P*-values were .27 for IGF-1, .11 for IGFBP-1, and .11 for IGFBP-2. Statistical results were significant if $P<.05$. All statistical analyses were conducted using R 2.5.1.[13]

RESULTS

There were no significant differences between the 625 participants and the rest of the Health ABC cohort in terms of race, sex, baseline age, weight, height, BMI, total percent fat, visceral fat, fasting insulin, fasting glucose, serum IL6, or serum CRP (results not shown). The median follow-up time for all 625 participants was 6.43 years (interquartile range 6.14–6.74 years), and 127 participants had died by the end of the study. Table 1 compares the basic demographic and biochemical measurements of participants who survived and those who had died by the end of the followup period. Baseline age, total percent fat, CRP, IL6, IGFBP-1, and IGFBP-2 were significantly different between these two groups. Other variables showed no significant differences between these two groups.

The associations between IGF-1, IGFBP-1, and IGFBP-2 and fasting glucose, fasting insulin, visceral fat, and total percent fat were examined (Table 2). In models that adjusted for baseline age, race, sex, and study site, higher IGFBP-1 and IGFBP-2 were associated with lower levels of fasting glucose, fasting insulin, visceral fat, and total percent fat. Higher IGF-1 was associated with higher fasting insulin.

Two sets of multivariate models were used to test the associations between IGF-1 and IGFBPs and survival. In the first set of models, the hazard ratio was adjusted for general demographic variables: race, sex, study site, and baseline age. In the second set of models, the hazard ratio was also adjusted for height, weight, visceral fat, total percent fat, fasting glucose, fasting

insulin, serum IL6, and serum CRP in addition to the basic demographic variables. In both sets of models, significant associations were found between high serum IGFBP-1 and IGFBP-2 and greater mortality (Table 3). Higher levels of IGFBP-1 and IGFBP-2 remained associated with greater mortality after adjusting for height, weight, visceral fat, total percent fat, fasting glucose, fasting insulin, serum IL6, and serum CRP. There was no significant association between IGF-1 and mortality. In models that included IGFBP-1 and IGFBP-2, both measurements remained significant predictors of mortality (result not shown).

DISCUSSION

These results demonstrate a strong association between higher IGFBP-2 and mortality and a somewhat weaker but still significant association between higher IGBP-1 and mortality in older adults. Surprisingly, it was found that higher IGFBP-1 and IGFBP-2 were associated with favorable risk factors, including lower fasting glucose and lower fasting insulin, but higher mortality. The association appears to be independent of acute-phase reactants (CRP and IL6) and significant after adjustment for fasting glucose, fasting insulin, and body fat.

Previous studies have demonstrated paradoxical effects of IGFBPs and cardiovascular risk factors and disease. One study found a strong association between higher IGFBP-1 levels and lower insulin levels, lower glucose levels, and lower adiposity.[9] Another study also noted an inverse association between serum IGFBP-1 and IGFBP-2 levels and insulin and body fat.[7] An association was found between higher IGFBP-1 and lower risk of impaired glucose tolerance in the Cardiovascular Health Study.[8] Thus, the association identified in the Health ABC Study between IGFBP-1 and IGFBP-2 and insulin, glucose levels, and body fat is consistent with multiple previous studies.

Despite its association with lower insulin resistance and body fat, higher IGFBP levels have been associated with greater mortality. An association was found between higher IGFBP-1 and greater cardiovascular and all-cause mortality in elderly men,[14] and an association was found between higher IGFBP-1 and greater risk of acute myocardial infarction in patients with type 2 diabetes mellitus.[15] An association between higher IGFBP-1 and higher all-cause mortality was identified in the Cardiovascular Health Study.[11] Higher IGFBP-1 levels were also found to be associated with greater risk of congestive heart failure and disability.[11,16] These results are consistent with IGFBP-1 as a marker of frailty and early mortality.[11] Higher IGFBP-1 was associated with lower insulin and glucose levels in the Cardiovascular Health Study[8]; thus, these results parallel the apparently paradoxical results with IGFBP-1 found in the current study. One study found an association between higher IGFBP-1 and lower mortality due to ischemic heart disease,[17] but that study found no association between IGFBP-1 and all cardiovascular mortality or all-cause mortality.

It has been shown that low serum IGFBP-2 level is an indicator of overall good physical function. Serum IGFBP-2 was negatively correlated with bone mineral density in Japanese postmenopausal women.[18] In men and women, IGFBP-2 tended to rise with age, and higher IGFBP-2 was associated with lower bone mineral density at most skeletal sites.[19] In healthy elderly men, high levels of serum IGFBP-2 were associated with higher degree of disability, lower physical performance, lower muscle strength, lower bone mineral density, lower lean mass, and lower fat mass.[20] No previous study has examined the association between IGFBP-2 and all-cause mortality in a healthy cohort. There are studies showing the relationship between IGFBP-2 and survival in patients with specific diseases. In patients with dilated cardiomyopathy, serum level of IGFBP-2 was significantly higher in nonsurvivors.[21] In women with ovarian cancer, higher levels of serum IGFBP-2 were significantly associated with poorer survival rate.[22]

The current study is consistent with a previous one[11] in demonstrating an association between higher IGFBP-1 and greater mortality. The current study is the first, to the authors' knowledge, to show an association between higher IGFBP-2 and greater all-cause mortality in a cohort study.

The results of this study and earlier studies on mortality and the results of the association between IGFBPs and disability suggest that the IGFBPs may be biomarkers of aging. Future cohort studies of disability and mortality in elderly people should also measure these factors. If the results are replicated in additional studies, these factors could be used as biomarkers of aging.

IGFBPs may have potentiating and inhibitory effects on IGF-1 activity.[23] At the tissue level, IGFBP-1 and IGFBP-2 may enhance IGF-1 binding to its receptors, thus potentiating IGF-1 activity.[6] Based on this interpretation, the higher IGFBP-1 and IGFBP-2 levels may be a marker of higher IGF-1 activity.

Studies of IGF-1 signaling and longevity in animal models have consistently demonstrated that lower IGF-1 signaling is associated with greater survival.[4] Lower IGF-1 signaling is also an adaptive response to deoxyribonucleic acid damage.[24] Thus, one explanation for the findings of the current study may be that IGFBP-1 and IGFBP-2 are markers of IGF-1 signaling and that higher levels of IGBP-1 and IGFBP-2 may indicate higher IGF-1 signaling in humans.

The mechanism of IGF-1 in animal models may explain the discordant effect of the IGFBPs on insulin resistance and mortality. Insulin receptor substrate 1 (IRS1) knockout mice have displayed several aspects of greater insulin resistance, although they also demonstrated delayed aging and were longer lived.[25] Mice with lower IRS2 signaling or lower IRS signaling in brain alone have recently been shown to have insulin resistance but also have greater stress resistance and longer life span.[26] These studies demonstrate that insulin resistance and delayed mortality can coexist. Thus, one potential explanation for the findings of the current study is that lower IGFBP-1 and IGFBP-2 levels are markers for lower IGF-1 signaling that are associated with the greater stress resistance seen in the IRS knockout models.

There are several limitations to the proposed interpretation. No association was found between IGF-1 and survival in this cohort, although more than 95% of IGF-1 is bound,[27] so it is possible that most of the functional variability in bioavailable IGF-1 is due to variability in its binding proteins. Higher IGFBP-1 and IGFBP-2 may be markers for another pathway not directly related to IGF-1 signaling. IGFBPs are known to be higher as part of the acute-phase reaction, [28] and components of the acute-phase reaction have been associated with greater mortality. Although CRP and IL6 were adjusted for in the analyses, it is possible that these adjustments did not capture other aspects of the acute inflammatory reaction, which may explain the association observed. Finally, it is possible that the association was due to a selection bias observed in this older healthy population because the subset of persons with lower IGFBP-1 and IGFBP-2 who were at highest risk were too ill to be considered eligible for the study.

The sample size and the small number of deaths in the 6 years of follow-up available in this cohort limited the analyses. Future studies of the effect of the other IGFBPs would also help to further understand the association between IGFBPs and mortality. In summary, a strong association between higher IGFBP-1 and IGFBP-2 levels and greater mortality in the Health ABC cohort have been identified.

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Table 1

Basic Clinical Measurements of 625 Participants and Comparison of Each Measurement Between the Survivor Group and Nonsurvivor Group

Clinical Measurement	Survived (n = 498)	Died (n = 127)	*P*-Value
White, %	60.0	48.0	.12
Male, %	47.4	58.3	.16
Baseline age, median (IQR)	73.0 (71.0–76.0)	74.0 (72.0–77.0)	.005
Body mass index, kg/m^2, mean ± SD	27.25 ± 4.77	26.90 ± 4.77	.46
Weight, kg, mean ± SD	75.37 ± 15.15	75.88 ± 14.70	.73
Height, cm, mean ± SD	166.1 ± 9.3	167.9 ± 9.1	.052
Fasting glucose, mg/dL, median (IQR)	94.0 (86.0–105.0)	95.0 (87.5–110.0)	.28
Fasting insulin (μIU/mL, median (IQR)	7.0 (5.0–9.9)	6.6 (4.8–10.1)	.48
Total percent fat, mean ± SD	34.97 ± 7.52	33.29 ± 8.24	.042
Visceral fat, cm^2, median (IQR)	129.0 (94.2–179.8)	128.0 (98.1–181.4)	.99
C-reactive protein, μg/mL, median (IQR)	1.48 (0.92–2.71)	2.34 (1.11–5.53)	<.001
Interleukin 6, pg/mL, median (IQR)	1.69 (1.22–2.47)	2.62 (1.65–4.00)	<.001
Insulin-like growth factor-1, ng/mL, mean ± SD (n = 623)	114.1 ± 40.1	116.6 ± 41.1	.53
IGFBP-1, ng/mL, median (IQR) (n = 610)	40.0 (23.3–65.0)	51.0 (28.8–90.0)	.007
IGFBP-2, ng/mL, median (IQR) (n = 621)	383.0 (247.0–598.5)	505.5 (297.8–789.8)	<.001

IGFBP = insulin-like growth factor 1 binding protein; IQR = interquartile range; SD = standard deviation.

Table 2

Association Between Insulin-Like Growth Factor-1 (IGF-1) and IGF Binding Proteins (IGFBPs) and Fasting Glucose, Fasting Insulin, Visceral Fat, and Total Percent Fat

	Linear Regression		Logistic Regression	
Outcome Variable	**Fasting Insulin (μIU/mL)**	**Total Percent Fat**	**Fasting Glucose (>101.0 mg/dL)**	**Visceral Fat (>171.2cm^2)**
	Coeffiecient ± SD			
IGF-1/SD	0.096 ± 0.028*	−0.085 ± 0.26	0.26 ± 0.14	0.10 ± 0.14
IGFBP-1/SD	−0.35 ± 0.022*	−2.31 ± 0.23*	−1.06 ± 0.18*	−1.53 ± 0.22*
IGFBP-2/SD	−0.29 ± 0.023*	−2.11 ± 0.23*	−0.86 ± 0.15*	−1.35 ± 0.19*

Note: Association was tested using linear regression or logistic regression models in which baseline age, sex, race, and study site were adjusted for as covariates. Insulin-like growth factor 1 (IGF-1), insulin-like growth factor 1 binding protein (IGFBP)-1, and IGFBP-2 were log transformed.

* $P<.001$.

SD = standard deviation.

Table 3

Association Between Insulin-Like Growth Factor- 1 (IGF-1) and IGF-1 Binding Proteins (IGFBPs) and Mortality

Outcome Variable	Basic Adjustment* Hazard Ratio (95% Confidence Interval) *P*-Value	Full Adjustment† Hazard Ratio (95% Confidence Interval) *P*-Value
IGF-1/SD	1.05 (0.88–1.27) .58	1.12 (0.91–1.37) .29
IGFBP-1/SD	1.28 (1.06–1.56) .01	1.34 (1.01–1.76) .04
IGFBP-2/SD	1.52 (1.27–1.82) <.001	1.48 (1.14–1.92) .003

*Adjusted for race, sex, study site, and baseline age.

†Adjusted for race, sex, study site, baseline age height, weight, visceral fat, total percent fat, fasting glucose, fasting insulin, serum interleukin 6, and serum C-reactive protein. IGF-1, IGFBP-1, and IGFBP-2 were log transformed.

SD = standard deviation.