Total Insulinlike Growth Factor 1 and Insulinlike Growth Factor Binding Protein Levels, Functional Status, and Mortality in Older Adults

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OBJECTIVES: To assess the association between total insulinlike growth factor (IGF)-1, IGF binding protein-1 (IGFBP-1), and IGFBP-3 levels and functioning and mortality in older adults.

DESIGN: Cohort study.

SETTING/PARTICIPANTS: One thousand one hundred twenty-two individuals aged 65 and older without prior cardiovascular disease events participating in the Cardiovascular Health Study.

MEASUREMENTS: Baseline fasting plasma levels of IGF-1, IGFBP-1, and IGFBP-3 (defined as tertiles, T1-T3) were examined in relationship to handgrip strength, time to walk 15 feet, development of new difficulties with activities of daily living (ADLs), and mortality.

RESULTS: Higher IGFBP-1 predicted worse handgrip strength (P-trend$_{T1\text{-}T3} < .01$) and slower walking speed (P-trend$_{T1\text{-}T3} = .03$), lower IGF-1 had a borderline significant association with worse handgrip strength (P-trend$_{T1\text{-}T3} = .06$), and better grip strength was observed in the middle IGFBP-3 tertile than in the low or high tertiles ($P = .03$). Adjusted for age, sex, and race, high IGFBP-1 predicted greater mortality (P-trend$_{T1\text{-}T3} < .001$, hazard ratio (HR)$_{T3vsT1} = 1.48$, 95% confidence interval (CI) = 1.15–1.90); this association was borderline significant after additional confounder adjustment (P-trend$_{T1\text{-}T3} = .05$, HR$_{T3vsT1} = 1.35$, 95% CI = 0.98–1.87). High IGFBP-1 was associated with greater risk of incident ADL difficulties after adjustment for age, sex, race, and other confounders (P-trend$_{T1\text{-}T3} = .04$, HR$_{T3vsT1} = 1.40$, CI = 1.01–1.94). Neither IGF-1 nor IGFBP-3 level predicted mortality or incident ADL difficulties.

CONCLUSION: In adults aged 65 and older, high IGFBP-1 levels were associated with greater risk of mortality and poorer functional ability, whereas IGF-1 and IGFBP-3 had little association with these outcomes.

Key words: disability; insulinlike growth factor (IGF); older adults

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Insulinlike growth factors (IGFs) constitute a highly conserved biological system that is hypothesized to be a key determinant of aging and longevity.[1] Model organisms with low IGF-1 activity have extended lifespans but may also have phenotypes associated with reduced fitness, including infertility, smaller body size, and metabolic abnormalities.[1–3] Aging in humans is associated with a decline in levels and activity of IGF-1, as well as changes in IGF binding proteins (IGFBPs). IGF-1 plays a central role in growth and development and also promotes muscle protein synthesis and cell proliferation and inhibits cell apoptosis. Declining IGF-1 with aging may contribute to loss of muscle strength and reduced physical performance in older adults. The most abundant IGFBP in serum is IGFBP-3, which serves as a circulating IGF-1 reservoir and may also have IGF-1–independent cell-survival and proliferation effects.[4,5] IGFBP-1 is an important regulator of IGF activity with inhibitory[6,7] and enhancing[8,9] actions on IGF-1. Circulating levels of IGFBP-1 are higher in older adults and in individuals exposed to stress,[10] inflammation,[11,12] muscle wasting,[13,14]

and nutritional deprivation.[15] High IGFBP-1 levels in catabolic conditions may reflect a pathophysiological state of inhibited IGF-1 bioactivity leading to reduced muscle protein synthesis.[16]

Well-conducted clinical trials have failed to show that growth hormone or IGF-1 treatment improves functional outcomes, morbidity, or mortality in elderly people,[17–19] although based on the recognition that IGF-1 may have trophic effects on muscle, several prior studies have examined whether circulating IGF-1 and IGFBP levels predict muscle strength and body composition in older adults. For example, in the Health, Aging and Body Composition Study cohort of men and women aged 70 to 79, low circulating IGF-1 levels were associated with reduced thigh muscle area and density.[20] Some studies have suggested an association between low IGF-1 and poorer outcomes on performance-based tests or self-reported measures of physical function,[21,22] whereas others have reported null findings.[23] Circulating IGF-1 and IGFBP levels have also been studied in relation to mortality[22,24–27] and other age-related diseases such as ischemic heart disease,[26] stroke,[28] and heart failure,[29] with mixed results.[30]

Whether fasting plasma total IGF-1, IGFBP-1, and IGFBP-3 levels were associated with declining ability to accomplish basic activities of daily living (ADLs) and mortality in men and women aged 65 and older was assessed. The association between IGF levels and performance-based tests of physical function, including voluntary handgrip strength and timed walk, was also examined.

METHODS

Study Population and Setting

The Cardiovascular Health Study (CHS) is a prospective population-based cohort study of cardiovascular disease (CVD) in a sample of 5,888 adults aged 65 and older living in four U.S. communities.[31] The original cohort of 5,201 participants was recruited in 1989 to 1990. In 1992 to 1993, 687 additional participants were recruited, almost all of whom were African American, to enhance the racial and ethnic diversity of the cohort. Potential subjects were identified from Medicare eligibility lists of then Health Care Financing Administration (HCFA) now called Centers for Medicare and Medicaid Services. Those eligible to participate included all persons living in the household of each individual sampled, who were aged 65 and older at the time of examination, expected to remain in the area for 3 years, and were able to give informed consent. Of those contacted and eligible, 57.3% were enrolled.

The present analyses of IGFs, functional status, and mortality were conducted in 1,122 CHS participants selected as comparison subjects in a nested case-cohort study of incident CVD events.[30] These individuals were selected at random from among CHS participants who were free of prior myocardial infarction (MI), stroke, or congestive heart failure at study baseline.

CHS participants completed standardized clinic examinations and questionnaires at study baseline and at nine annual follow-up visits. Data collection included fasting blood collection for laboratory tests; performance-based measurements of physical function; clinical measurements, including height, weight, blood pressure, and electrocardiogram (ECG); noninvasive assessment of the carotid arteries; an inventory of currently used medications; and an interviewer-administered assessment of medical history, health-related behaviors, and demographic and socioeconomic factors.

Study Measurements

Handgrip strength in the dominant hand was measured as the average of three grip strength attempts using a handheld Jamar dynamometer (Asimow Engineering Co., Los Angeles, CA). Subjects completed a timed 15-foot (4.572 m) walk at normal pace. At baseline and during each annual follow-up contact, CHS participants reported whether they had difficulties with ADLs, including walking around the home, getting out of bed, eating, dressing, bathing, and using the toilet, or with instrumental ADLs (IADLs), including heavy housework, light housework, shopping, preparing meals, paying bills, and using the phone. Laboratory measurements of fasting lipids and glucose were made at the core CHS laboratory.[32] For CHS participants included in the present study, plasma specimens that had been collected at CHS baseline after overnight fasting and maintained at -70°C storage were sent to the Cancer Prevention Research Unit, Lady Davis Research Institute of Jewish General Hospital for analyses of total IGF-1, IGFBP-1, and IGFBP-3 using enzyme-linked immunosorbent assay methods (Diagnostics Systems Laboratory, Webster, TX), as previously described.[30] All measurements were performed in duplicate. Within-batch and between-batch coefficients of variation (CVs) derived from a control pool of 214 participants from the present study were 6.9% and 6.0% for IGF-1, 3.5% and 3.1% for IGFBP-1, and 6.0% and 3.6% for IGFBP-3, respectively. To assess within-individual stability of IGF levels over time, repeated measures were conducted over 2 to 3 years in a subset of participants; Pearson correlation coefficients (r) were found of 0.74 for IGFBP-1, 0.83 for IGF-1, and 0.83 for IGFBP-3.[30] For 50 individuals, assays were replicated at the Cancer Prevention Research Unit, Lady Davis Research Institute and at two outside laboratories; between-laboratory correlation coefficients for IGF-1 levels were 0.95 to 0.97.

Identification of Incident Events and Mortality

During follow-up, all incident CVD events, hospitalizations, and deaths were identified through semiannual participant contacts, notification of events by participants and proxies, and periodic searches of national administrative databases (e.g., HCFA Medicare utilization database, National Death Index).[33] Medical records for all deaths and incident CVD events were centrally reviewed and classified.

Variable Definition

Data from the baseline CHS examination were used in these analyses, with the exception of follow-up data on ADL and IADL abilities and mortality. Use of medications, including antihypertensive medications, medications for diabetes mellitus, oral estrogens, thyroid hormones, oral steroids, and diuretics, was defined according to the baseline medication inventory.

Diabetes mellitus status was defined according to measured fasting glucose levels or self-reported history of drug-

treated diabetes mellitus. Clinical CVD was defined as angina pectoris, angioplasty, bypass surgery, or coronary artery angioplasty. Subclinical CVD measures included carotid artery stenosis and wall thickness, left ventricular hypertrophy (LVH) and other ECG findings, and ankle-arm blood pressure index. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Self-reported general health status was recorded as poor, fair, good, very good, or excellent.

Statistical Analyses

In preliminary analyses, distributions of IGF-1, IGFBP-1, and IGFBP-3 were examined to identify outlying values. The interrelationship between IGF-1 and IGFBP levels was assessed using Pearson correlations and linear regression. To address the question of whether IGF-1 and IGFBP levels were associated with functional status and mortality, three analyses were performed. First, cross-sectional analyses examined the association between baseline IGF levels and handgrip strength and time to complete the timed walk, with linear regression used to adjust for age and other confounders. Second, the association between baseline IGF levels and mortality was examined. Third, in 859 CHS participants who reported no difficulties with ADLs or IADLs at baseline, the association between baseline IGF levels and the future development of one or more ADL or IADL difficulties at follow-up visits was examined. The prospective analyses of incident mortality, ADL difficulties, and IADL difficulties used multivariate Cox proportional hazard regression models to estimate adjusted hazard ratios (HRs). Associations were estimated for tertiles of IGF values (T1-T3), with the lowest tertile as the reference group and with category cutpoints defined according to the distributions in the overall CHS subcohort (tertile cutpoints were 121.1 and 170.9 μg/L for IGF-1, 19.8 and 36.9 μg/L for IGFBP-1, and 3,651.2 and 4,419.7 μg/L for IGFBP-3). Statistical tests were derived based on linear trends across tertiles (P-trend$_{T1\text{-}T3}$). To assess the possibility of nonlinear associations, comparisons between individual tertiles were evaluated, and further statistical testing was used to explore for nonlinear (quadratic) trends across tertiles. Quadratic models were nonsignificant except where indicated in the Results (specifically, analyses of IGFBP-3 and handgrip strength). To exclude the possibility of outlier effects, analyses were repeated after excluding subjects in the upper 5% of the distribution of IGF-1 and IGFBPs, which did not change the overall results appreciably. Adjustment variables identified from prior CHS analyses of independent predictors of declining physical function[34] and mortality[35] were forced into regression models. ADL difficulty and IADL difficulty analyses were also adjusted for handgrip strength and walk time to see whether these intermediate variables explained the association between IGFs and functional limitation. To assess the effect of preexisting poor health on the prospective associations between IGF levels and mortality and incident ADL and IADL difficulties, analyses were repeated after excluding subjects with self-reported fair or poor health (n = 225 (n = 30 poor health, n = 195 fair health)), BMI less than 18.5 kg/m^2 (n = 22), and low level of educational attainment (less than a high school education, n = 320). Because circulating counter-regulation by insulin of hepatic IGFBP-1 secretions strongly affects IGFBP-1 levels, analyses assessing IGFBP-1 and handgrip strength, timed walk, incident ADL and IADL difficulties, and total mortality were repeated excluding participants reporting insulin use at baseline (n = 29); this did not significantly affect the results. Missing values were present in 4% or fewer of subjects for all variables except income (missing = 6.6%). The complete-case approach was used to handle missing values (i.e., all subjects with missing variables were excluded from models that included these variables).[36]

RESULTS

Included in the analyses were 1,122 subjects randomly selected from among CHS participants who were free of prior MI, stroke, or CHF at study baseline (Table 1). Mean age at baseline was 72.4 (range 64–92). Age had an inverse correlation with total IGF-1 ($r = -0.11$, $P < .001$) and IGFBP-3 ($r = -0.17$, $P < .0001$) and a positive correlation with IGFBP-1 ($r = 0.20$, $P < .001$). Correlation coefficients were -0.23 ($P < .001$) between total IGF-1 and IGFBP-1, 0.62 ($P < .001$) between total IGF-1 and IGFBP-3, and -0.14 ($P < .001$) between IGFBP-1 and IGFBP-3. Quadratic terms relating IGF-1 levels with IGFBP levels were not significant, suggesting that these associations were essentially linear.

Handgrip Strength

Adjusted for age, sex, race, income, clinical and subclinical CVD, diabetes mellitus, BMI, hypertension treatment, blood pressure, education, alcohol intake, and smoking, analyses suggested a possible association between higher baseline total IGF-1 level and higher handgrip strength, although this finding did not reach the $P < .05$ level of statistical significance (P-trend$_{T1\text{-}T3} = .06$) (Figure 1). Higher IGFBP-1 level had a significant, independent association with worse handgrip strength (P-trend$_{T1\text{-}T3} < .01$). The adjusted difference in handgrip strength comparing extreme IGFBP-1 tertiles was 1.6 kg. In the same models, it was estimated that the magnitude of the difference between extreme IGFBP-1 tertiles was similar to the effect of 4 years of aging (i.e., handgrip strength decreased 0.4 kg with each additional year of age). IGFBP-3 level had a significant U-shaped relationship with handgrip strength, with approximately 1 kg higher handgrip strength in individuals in the middle IGFBP-3 tertile than in those in the low or high IGFBP-3 tertiles ($P = .03$ for quadratic analyses of handgrip strength across tertiles).

Walking Speed

Performance on the timed 15-foot walk was not significantly associated with IGF-1 levels (P-trend$_{T1\text{-}T3} = .16$) (Figure 2). The association between higher IGFBP-1 and slower walking speed was statistically significant (P-trend$_{T1\text{-}T3} = .03$). Using the observed association between walking speed and age in the same models, it was estimated that the difference in walking speed between extreme IGFBP-1 tertiles was of similar magnitude to the difference associated with 4 years of age. IGFBP-3 level was not associated with walking speed.

Table 1. Characteristics at Baseline Study Visits of 1,122 Cardiovascular Health Study Participants Without Prior Cardiovascular Events

Characteristic	Results	
Age, n (%)		
65–69	426	(38.0)
70–74	349	(31.1)
75–79	224	(20.0)
80–84	89	(7.9)
85–89	24	(2.1)
≥90	10	(0.9)
Race, n (%)		
Non-Hispanic white	908	(80.9)
Other	214	(19.1)
Sex, n (%)		
Male	397	(35.4)
Female	725	(64.6)
Number of difficulties with activities of daily living, n (%)*		
0	1,040	(92.8)
1	50	(4.5)
2	21	(1.9)
3	6	(0.5)
4	3	(0.3)
5	1	(0.1)
Number of difficulties with instrumental activities of daily living, n (%)†		
0	874	(77.8)
1	183	(16.3)
2	34	(3.0)
3	16	(1.4)
4	10	(0.9)
5	2	(0.2)
6	2	(0.2)
Self-reported general health status, n (%)		
Excellent	73	(7.7)
Very good	307	(32.5)
Good	405	(42.9)
Fair	150	(15.9)
Poor	10	(1.1)
Education level, n (%)		
Less than high school	320	(28.6)
High school graduate	798	(71.4)
Income, $, n (%)		
<25,000	640	(61.1)
25,000–49,999	270	(25.8)
≥50,000	138	(13.2)
Diabetes mellitus status, n (%)		
Normal	821	(73.4)
Impaired fasting glucose	148	(13.2)
Diabetic	150	(13.4)
Smoking status, n (%)		
Never smoker	543	(48.4)
Former smoker	446	(39.8)
Current smoker	132	(11.8)
Alcohol use, drinks/wk, n (%)		
0	538	(48.4)
≤7	442	(39.8)
>7	132	(11.9)
Clinical cardiovascular disease, n (%)	142	(12.7)
Maximal carotid artery stenosis, n (%)		
Normal	384	(34.8)
<25%	395	(35.8)
25–49%	284	(25.7)
⩾50%	41	(3.7)
Estrogen use, n (%)	88	(7.8)
Thyroid hormone use, n (%)	89	(7.9)
Oral steroid use, n (%)	28	(2.5)
Diuretic use, n (%)	305	(27.2)
Any major electrocardiogram abnormality, n (%)	264	(24.2)
Left ventricular hypertrophy according to electrocardiogram, n (%)	47	(4.3)
Handgrip strength, kg, mean ± SD (range)	27.7 ± 10.5	(1.4–90.0)
Time to complete 15-foot walk, seconds, mean ± SD (range)	5.8 ± 2.5	(3.0–50.0)
Walking speed, m/s, mean ± SD (range)	0.79 ± 1.82	(0.09–1.52)
Body mass index, kg/m^2, mean ± SD (range)	26.9 ± 5.1	(15.0–58.8)
Ankle-brachial index, mean ± SD (range)	1.1 ± 0.2	(0.4–1.6)
Maximal thickness of internal carotid artery, mm, mean ± SD (range)	1.4 ± 0.7	(0.6–4.7)
Weight, kg, mean ± SD (range)	72.4 ± 15.4	(32.8–146.5)
Physical activity, kcal/wk, mean ± SD (range)	1,831.1 ± 2,190.3	(0–14,625.0)
Fasting glucose, mg/dL, mean ± SD (range)	109.6 ± 36.8	(68.6–657.0)
Albumin, g/dL, mean ± SD (range)	4.0 ± 0.3	(3.1–4.9)
Creatinine, mg/dL, mean ± SD (range)	1.0 ± 0.4	(0.5–10.0)
Digit Symbol Substitution Test score, mean ± SD (range)	37.2 ± 13.4	(0–88.0)
Systolic blood pressure, mmHg, mean ± SD (range)	137.0 ± 22.0	(87.0–230.0)
Diastolic blood pressure, mmHg, mean ± SD (range)	71.6 ± 11.6	(30.0–113.0)
IGF-1, μg/L, mean ± SD (range)	152.3 ± 58.5	(29.3–496.9)
IGFBP-1, μg/L, mean ± SD (range)	31.3 ± 20.0	(0.9–115.9)
IGFBP-3, μg/L, mean ± SD (range)	4,045.7 ± 902.9	(1,374.3–7,800.0)

(*Continued*)

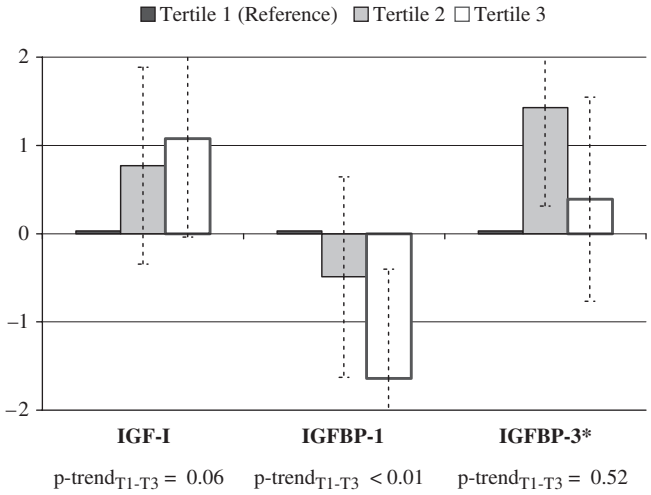
Table 1. (Contd.)

* Walking around the home, getting out of bed, eating, dressing, bathing, and using the toilet.

† Heavy housework, light housework, shopping, preparing meals, paying bills, using the phone.

Prevalent clinical cardiovascular disease includes angina, angioplasty, bypass surgery or coronary artery angioplasty before baseline examination.

SD = standard deviation; IGF = insulinlike growth factor; IGFBP = IGF binding protein.



*For IGFBP-3, a nonlinear (quadratic) model relating IGFBP-3 tertile with handgrip strength was statistically significant ($P = .03$).

Figure 1. Association between levels of total insulinlike growth factor (IGF)-1, IGF binding protein (IGFBP)-1, and IGFBP-3 and handgrip strength at baseline study visit. Beta coefficients derived from linear regression of IGF-1, IGFBP-1, IGFBP-3, and adjustment variables on the dependent variable of handgrip strength. Adjusted for age, sex, race, income, clinical and subclinical cardiovascular disease, diabetes mellitus, body mass index, hypertension or blood pressure, education, alcohol use, and smoking. Tertile cutpoints were 121.1 and 170.9 μg/L for IGF-1, 19.8 and 36.9 μg/L for IGFBP-1, and 3,651.2 and 4,419.7 μg/L for IGFBP-3. *Y* axis, adjusted difference in handgrip strength in kg (vs Tertile 1). Dotted lines represent 95% confidence intervals.

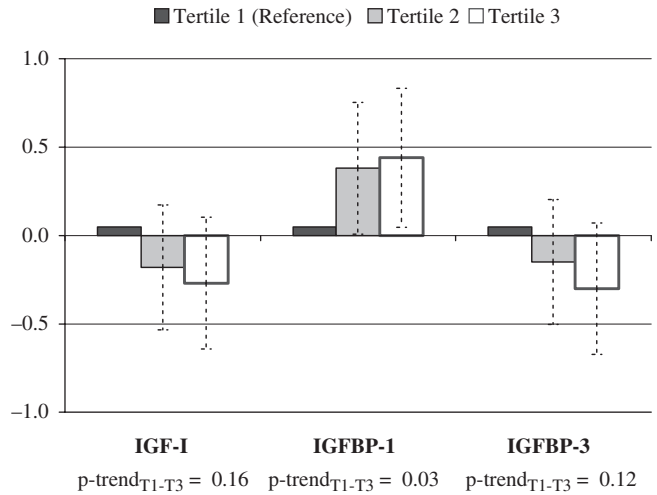


Figure 2. Association between levels of total insulinlike growth factor (IGF)-1, IGF binding protein (IGFBP)-1, and IGFBP-3 level with time to complete 15-foot walk at baseline study visit. Beta coefficients derived from linear regression of IGF-1, IGFBP-1, IGFBP-3, and adjustment variables on the dependent variable of time to walk 15 feet (4.572 m) at usual pace. Adjusted for age, sex, race, income, clinical and subclinical cardiovascular disease, diabetes mellitus, body mass index, hypertension or blood pressure, education, alcohol use, and smoking. Tertile cutpoints were 121.1 and 170.9 μg/L for IGF-1, 19.8 and 36.9 μg/L for IGFBP-1, and 3,651.2 and 4,419.7 μg/L for IGFBP-3. *Y* axis, adjusted difference in time to complete 15-foot walk, in seconds (vs Tertile 1). Dotted lines represent 95% confidence intervals.

Mortality

During 8 years of follow-up, 398 of the 1,122 CHS participants included in this study died. Adjusted for age, sex, and race, an association between higher IGFBP-1 levels and greater mortality was observed, with P-trend$_{T1-T3} < .001$ for mortality risk across IGFBP-1 tertiles (Table 2). Examination of individual tertiles suggested that the greater risk appeared to be limited to the highest IGFBP-1 tertile (HR for T3 vs T1 = 1.48, 95% confidence interval (CI) = 1.15–1.90). After additional adjustment for income, clinical and subclinical CVD, weight, physical activity, smoking, diuretic use, glucose, albumin, creatinine, general health status, difficulties with IADLs, and digit symbol substitution test, results were attenuated slightly and were of borderline significance (P-trend$_{T1-T3} = .05$). In further analyses, the association between IGFBP-1 level and CVD-related deaths (n = 130) and non-CVD-related deaths (n = 265) was found to be consistent with the results for overall mortality (data not shown). Analyses were repeated after exclusion of individuals with preexisting difficulties with ADLs or IADLs, fair or poor health status, BMI less than 18.5, and low level of education, and results were found to be similar but somewhat attenuated and nonsignificant. No association was apparent between baseline IGF-1 or IGFBP-3 level and total, CVD, or non-CVD mortality.

Incident Difficulties with Daily Activities

For analyses of incident difficulties with daily activities, individuals with any ADL or IADL difficulties at baseline were excluded. (Mean levels in μg/L in included subjects were IGF-1, 153.5; IGFBP-1, 30.9; IGFBP-3, 4,051.5. Mean levels in μg/L in excluded subjects were IGF-1, 148.2; IGFBP-1, 32.7; IGFBP-3, 4,022.0.) Of 859 subjects without any ADL or IADL difficulties at baseline, 318 developed new ADL difficulties, and 470 developed new IADL difficulties during follow-up. Models adjusted for age, sex, and race suggested no association between baseline IGFBP-1 level and risk of developing incident difficulties with ADLs (Table 3). After further adjustment for income, education, clinical and subclinical CVD, diabetes mellitus, fasting glucose, BMI, blood pressure, treatment for hypertension, alcohol intake, and smoking, the association between IGFBP-1 level and risk of developing incident difficulties with ADLs was significant (P-trend$_{T1-T3} = .04$) (Table 3). In these models, the greater risk of developing ADL difficulties appeared to be limited to individuals in the highest IGFBP-1 tertile (HR for T3 vs T1 = 1.40, 95% CI = 1.01–1.94). Results were attenuated slightly, and P-values were higher after adjustment for handgrip strength (P-trend$_{T1-T3} = .10$, HR for T3 vs T1 = 1.32) and walking speed (P-trend$_{T1-T3} = .05$, HR for T3 vs T1 = 1.38). Analyses were repeated after excluding individuals with self-reported fair or poor health, BMI less than 18.5, or low education, which reduced the number of incident events by approximately half; this produced similar results but with wider CIs (HR for T3 vs T1 = 1.32, 95% CI = 0.87–2.01) and a nonsignificant P-value (P-trend$_{T1-T3} = .18$). In contrast to results for IGFBP-1, the hazard of developing incident difficulties with ADLs did not vary according to

Table 2. Total Insulinlike Growth Factor (IGF)-1, IGF Binding Protein (IGFBP)-1, and IGFBP-3 Levels as Predictors of Mortality in 1,122 Cardiovascular Health Study Participants Free of Prior Cardiovascular Disease Events

Data	Tertile of Predictor Variable			*P*-Trend$_{T1-T3}$
	1	2	3	
IGF-1				
Deaths, n	147	123	128	
Mortality per 1,000 PY	42.3	33.6	35.8	
HR (95% CI) adjusted for age, sex, and race	1 (reference)	0.79 (0.62–1.01)	0.90 (0.70–1.14)	.37
Multivariate-adjusted HR (95% CI)*	1 (reference)	0.85 (0.65–1.12)	0.84 (0.63–1.11)	.22
IGFBP-1				
Deaths, n	105	121	172	
Mortality per 1,000 PY	29.0	32.8	52.4	
HR (95% CI) adjusted for age, sex, and race	1 (reference)	0.98 (0.75–1.27)	1.48 (1.15–1.90)	<.001
Multivariate-adjusted HR (95% CI)*	1 (reference)	0.95 (0.70–1.29)	1.35 (0.98–1.87)	.05
IGFBP-3				
Deaths, n	153	127	118	
Mortality per 1,000 PY	46.2	34.9	31.3	
HR (95% CI) adjusted for age, sex, and race	1 (reference)	0.86 (0.68–1.10)	0.85 (0.66–1.09)	.19
Multivariate-adjusted HR (95% CI)*	1 (reference)	0.81 (0.62–1.06)	0.83 (0.62–1.11)	.18

* Multivariate Cox proportional hazards regression adjusted for age, sex, race, income, clinical and subclinical cardiovascular disease, weight, physical activity, smoking, diuretic, glucose, albumin, creatinine, general health status, difficulties with instrumental activities of daily living, and Digit Symbol Substitution Test score.

Tertile cutpoints were 121.1 and 170.9 μg/L for IGF-I, 19.8 and 36.9 μg/L for IGFBP-1, and 3,651.2 and 4,419.7 μg/L for IGFBP-3.

PY = person years; HR = hazard ratio; CI = confidence interval.

baseline total IGF-1 or IGFBP-3 level. Adjusted for age, sex, race, and other confounders, compared with the lowest IGF-1 tertile, the adjusted HR was 1.03 (95% CI = 0.77–1.39) for the second IGF-1 tertile and 1.10 (95% CI = 0.82–1.47) for the highest IGF-1 tertile (P-trend$_{T1-T3}$ = .53). Compared with the lowest IGFBP-3 tertile, the adjusted HR was 1.09 (95% CI = 0.81–1.46) for the second IGFBP-3 tertile and 1.03 (95% CI = 0.75–1.40) for the highest IGFBP-3 tertile (P-trend$_{T1-T3}$ = .88). IGF-1, IGFBP-1, and IGFBP-3 levels were not associated with risk of developing difficulties with IADLs.

DISCUSSION

It has been hypothesized that the IGF-1/IGFBP axis contributes to declining muscle strength and other functional impairments with aging, although recent clinical trials of interventions to increase IGF-1 levels in older adults have not produced improvements in functioning.[17–19] In this observational study of adults aged 65 and older, the risks of dying and of developing new difficulties with ADLs were 30% to 50% higher in those in the highest tertile of fasting IGFBP-1 levels (>36.9 μg/L) than in those in the lowest IGFBP-1 tertile (<19.8 μg/L). High IGFBP-1 level was also associated with poorer handgrip strength and slower walking speed, with the magnitude of observed differences between extreme IGFBP-1 tertiles similar to the effect of 4 years of aging on these functional measures. Low levels of total IGF-1 had a marginal association with weaker handgrip strength, but total IGF-1 levels did not predict walking speed, incident decline in functional status, or mortality. IGFBP-3 appeared to have a U-shaped association with

Table 3. Insulinlike Growth Factor Binding Protein (IGFBP)-1 Levels as Predictors of New Difficulties with Activities of Daily Living (ADLs) in 859 Cardiovascular Health Study Participants Free of Prior Cardiovascular Events with No Preexisting ADL or Instrumental ADL Difficulties

Data	IGFBP-1 Tertile			*P*-Trend$_{T1-T3}$
	1	2	3	
Number with incident ADL difficulties	102	100	116	
Rate per 1,000 PY	46.03	41.06	53.27	
HR (95% CI) adjusted for age, sex, and race	1 (reference)	0.87 (0.66–1.15)	1.07 (0.81–1.41)	.60
Multivariate-adjusted HR (95% CI)*	1 (reference)	0.98 (0.72–1.35)	1.40 (1.01–1.94)	.04

* Multivariate Cox proportional hazards regression models adjusted for age, sex, race, income, clinical and subclinical cardiovascular disease, diabetes mellitus, body mass index, hypertension or blood pressure, education, alcohol use, and smoking.

IGFBP-1 tertile cutpoints were 19.8 and 36.9 μg/L.

PY = person years; HR = hazard ratio; CI = confidence interval.

handgrip strength, with the best handgrip performance observed in individuals in the middle IGFBP-3 tertile, although other study outcomes were not associated with IGFBP-3 levels. Overall, the data suggest that IGFBP-1 may be a more informative marker than IGF-1 or IGFBP-3 for predicting functional outcomes and survival in elderly people.

Prior studies have produced conflicting evidence regarding the association between circulating IGF-1 and IGFBP levels and body composition, physical function, metabolic variables, and other measures in older adults.[21,23] In a cross-sectional analysis from the Women's Health and Aging Study (WHAS) of women aged 70 to 79, lower total IGF-1 level was correlated with poorer performance on timed walk and chair stand tasks and lower knee extensor strength but not with handgrip or hip flexor strength.[22] In the WHAS, low IGF-1 was associated with self-reported difficulties with some physical tasks (getting in and out of a chair, walking steps) but not with others (lifting and carrying 10 lb, walking 2–3 blocks, heavy housework). In older adults in the Framingham Heart Study, lower baseline IGF-1 level predicted greater loss in fat free mass (FFM) over 2 years in men, although IGF-1 was unrelated to changes in FFM in women.[37] In the Health, Aging and Body Composition Study cohort, low IGF-1 level was correlated cross-sectionally with low thigh muscle area and density but did not predict prospective changes in body composition in older adults.[20] Prior reports from elderly populations, including studies from the Karolinska,[38] Rotterdam,[39] and Seven Countries Study[40] groups and the CHS cohort,[41] have shown an inverse association between fasting IGFBP-1 and levels of obesity, insulin, glucose, and other features of the metabolic syndrome, whereas associations between these characteristics and total IGF-1 levels have been less consistently demonstrated.[39,41,42] With regard to all-cause mortality, the Framingham study identified low baseline IGF-1 as an important independent predictor,[24] although the current study and others have not replicated this finding (e.g., WHAS,[22] National Health and Nutrition Examination Survey,[25] Rancho Bernardo,[26] Seven Countries[27]). The lack of data on trajectories of IGF-1 levels over time limited nearly all of these prior studies.

Circulating IGFBP-1 levels increase in catabolic conditions such as cachexia, malnutrition, and trauma,[10,13–15] and proinflammatory cytokines including interleukin-6 and tumor necrosis factor-α stimulate hepatic production of IGFBP-1.[11,12] In the present study population, the upper tertile of IGFBP-1 (>36.9 μg/L) appeared to identify a group of older adults at greater mortality risk. The IGFBP-1 levels that were used to define the upper tertile were relatively low (approximately half or less) compared with the mean IGFBP-1 levels observed in healthy subjects undergoing caloric restriction[43] and in patients with acquired immunodeficiency syndrome with wasting.[14] IGFBP-1 was also found to predict poorer handgrip strength and walking speed, as well as severe disability as measured according to incident difficulties with ADLs. IGFBP-1 did not predict the development of less-severe disability as measured according to difficulty with IADLs. Thus, this study suggests that high IGFBP-1 levels may be an adverse prognostic factor in apparently healthy older adults, which has not been previously reported. In the Rancho Bernardo cohort, high IGFBP-1 levels were associated with lower risk of ischemic heart disease mortality, although results for nonischemic heart disease or all-cause mortality were null.[26] IGFBP-1 levels in the Rancho Bernardo study were nonfasting, which makes interpretation of these results uncertain because of the dynamic regulation of IGFBP-1 levels by diet and insulin levels. No association between fasting IGFBP-1 level and mortality was reported in men aged 70 to 89 in the Seven Countries Study, although the sample size in that study was small ($n = 355$), and blood specimens were maintained at -20°C rather than at more optimal -70°C conditions as in the present study.[44]

Whether the present data reflect a causal relationship between IGFBP-1 and physical function and survival is unclear. Although IGFBP-1 appears to be an important regulator of IGF-1, the effect of circulating IGFBP-1 on IGF-1 activity is incompletely understood. In plasma, IGFBP-1 is inversely associated with concentration of free IGF-1, and IGFBP-1 has inhibitory actions on IGF-1.[6,7] Thus, high IGFBP-1 may indicate lower bioavailability of circulating IGF-1 and inhibition of anabolic IGF-1 effects. Inhibitory effects of IGFBP-1 on muscle protein synthesis have been shown in the rat in the basal state and in the presence of high IGF-1.[16] This effect of acute IGFBP-1 infusion on muscle synthesis appears to be due to reduced translational efficiency mediated by direct effects of IGFBP-1 or through reduction of free IGF-1 rather than due to a stress response, generalized energy deficit, or changes in other anabolic hormones such as insulin.[16] In contrast, other studies show that IGFBP-1 can also enhance the growth-promoting activity of IGF-1.[8,9] Further studies to characterize IGFBP-1 actions are needed to explain the finding that IGFBP-1, but not total IGF-1, was associated with age-related phenotypes. It is also important to note that the relationship between circulating IGF-1 and IGFBP levels and levels in muscle and other tissues is uncertain.

The prospective nature of this study is a strength, because it is among a small number of large prospective studies to relate IGF-1 and IGFBP levels to risk of incident functional decline and mortality in an elderly population. IGF-1 and IGFBP levels are known to change over time, and measurements in a single baseline plasma sample were relied upon to characterize individuals during 8 years of follow-up, although a substudy found that within-individual correlations over time in levels were good over 2 to 3 years. IGFBP-1 levels decrease dramatically with food ingestion because of the insulin-dependent regulation of hepatic IGFBP-1. Therefore, the availability of overnight fasting specimens in the CHS is a considerable strength. A limitation of the present analysis is the lack of data on free IGF-1 levels, because prior studies suggest that free IGF-1 may be more informative than total IGF-1 levels in predicting age-related outcomes.[21,39,45] Because IGF levels may differ according to race,[46] it is important to note that the CHS population was predominantly white, which limits the generalizability of the results to nonwhite populations. In addition, this study was limited to individuals without prior MI, stroke, or CHF, which limits the ability to generalize the results to the broader population of older adults. These findings relating IGFBP-1 levels to mortality and physical function are novel and will require replication.

In summary, in CHS participants aged 65 and older without prior CVD events, those with high IGFBP-1 levels

had lower voluntary handgrip strength and slower walking speed and were at greater risk of developing new functional limitations and death, independent of other demographic, clinical, and behavioral risk factors. Low total circulating IGF-1 level was a weak predictor of low handgrip strength but was unrelated to the development of functional limitations or death. This study provides limited support for the hypothesis that changes in the IGF system may play a role in functional decline and mortality in older adults, and the findings indicate that further study of IGFBPs, and IGFBP-1 in particular, may increase understanding of the physiology of aging. From a clinical perspective, the results need to be interpreted cautiously in light of completed randomized, clinical trials showing no improvement in muscle strength and other outcomes after increasing circulating IGF-1 levels using growth hormone supplementation.[17–19]

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