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IGF-1 and IGFBP-1 and Cognitive Function in Older Men and Women

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Abstract

Context—Both IGF-1 and cognition decrease with age. IGF-1 is positively associated with cognitive function in individuals with dementia and Alzheimer's disease, but results are inconsistent for healthy individuals.

Objective—To assess the association of IGF-1 and IGFBP-1 with three cognitive function tests in a healthy elderly population

Design, Setting, Patients or Other Participants—Men (636) and women (899) from the Rancho Bernardo study (median age 74 years) were assessed in the period between 1988 and 1992 for cognitive function through administering the Mini-Mental State Exam (MMSE), Verbal Fluency (VF), and Trails B tests. Blood samples were obtained at the same time for IGF-1 and IGFBP-1 levels. We assessed the association between biomarkers and cognitive function tests by dichotomizing tests at the clinically-relevant cut-off using logistic regression and by tertiles and continuous IGF-1 and IGFBP-1 levels using multivariate linear regression analyses.

Results—The mean MMSE, VF and Trails B test scores showed better cognitive function with higher IGF-1 tertiles. In multivariate analyses we found verbal fluency and MMSE were each significantly associated with IGF-1 in a dose-response manner for men (P for trend = 0.001), but no cognitive function tests were related to IGF-1 in women. For men, the highest IGFBP-1 tertile was inversely and significantly different from the lowest tertile for the MMSE test only (P for trend =0.02).

Conclusions—IGF-1 was independently and positively related to MMSE and VF in men and IGFBP-1 was inversely associated with MMSE in men. Sex differences in the association needs further investigation.

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Author Contributions

- **Wael Al-Delaimy:** study concept and design; formulation of analysis plan; interpretation of findings; and preparation of manuscript.
- **Denise Von Muhlen:** analysis of data; interpretation of findings; and critical revision of manuscript.
- **Elizabeth Barrett-Connor:** acquisition of data; interpretation of findings; overall study conception and design; and critical revision of manuscript.

Conflict of Interests

a. *Financial conflicts:* None

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Keywords

cognitive function; IGF-1; IGFBP-1

Introduction

There is almost unanimous agreement that IGF-1 declines in serum with increasing age [1, 2]. Increasing age is strongly related to decline in cognition and some studies have found an association between the decreasing levels of IGF factors and a decline in cognitive functions in older individuals [1, 3]. Although circulating IGF-1 is closely related to growth hormones, IGF-1 can also be synthesized locally in the brain, where it is not under the control of growth hormones and is concentrated in neuron-rich brain structures. It is believed that IGF-1 promotes glucose uptake in brain tissue and is related to neuronal growth [4]. The IGF-1 receptors in the brain have been found in abundance in the areas responsible for cognition, such as the hippocampus, as well as in the prefrontal cortex [1]. IGF-1 infusion in rats caused a significant three-fold increase in neuronal production, suggesting an important regulatory role in neurogenesis; this might explain age-related decline in cognition with the decline of IGF-1 [5].

In human studies, the evidence is generally supportive of a neurorprotective effect. Aleman et al [6] found a close correlation between serum IGF-1 levels of 25 healthy men (mean age 69 years) with age-sensitive cognitive functions, such as digit symbol substitution test and concept shifting task. This was established in other studies as well [7, 8]. Furthermore, lower serum levels of IGF-1 have been found to correlate significantly with a decline in mini-mental status examination scores [9–11]. There was also better performance of spatial memory, spatial ability, and verbal fluency with higher IGF-1 levels [12]. Recent studies among middle-aged men [13] and women [14] suggested an association between IGF or their binding proteins with telephone-interview cognitive function tests. However, an intervention study of IGF-1 injections did not improve memory tests in an elderly population [15].

There is a need for further studies in healthy elderly adults on the association of IGF-1 with cognitive function, as a precursor to possible tests of its use for prevention of cognitive decline in old age. Furthermore, the influence of sex on IGF-1 and related hormones and its association with cognitive function is not well studied. The Rancho Bernardo study provided an opportunity to address this association in community-dwelling relatively healthy older adults who would be expected to show some age-related decline in both cognitive function tests and IGF-1.

Methods

The Rancho Bernardo study began between 1972 and 1974 as a population-based heart disease risk-factor screening survey for residents who lived in the Southern California community of Rancho Bernardo. A total of 82% of all adult residents aged 30–79 years enrolled in the survey, which included demographic data and lifestyle habits of the participants. Participants were mostly white, middle- to upper-middle class, and well educated. They have been followed up for vital status with annual mailed surveys and invited for detailed follow up clinic visits every few years.

In the period between 1988 and 1992, 80% (n=1727) of the surviving men and women from this cohort were invited to a follow-up clinic visit. A questionnaire on demographic and lifestyle factors was administered, cognitive function tests were performed by a specially-trained nurse, and venous blood samples were drawn. As a result, 899 women and 636 men had their blood analyzed for IGF-1 and IGFBP-1 and had cognitive function tests conducted at the same time.

All participants gave written informed consent and the study protocol was approved by the institutional review board of University of California, San Diego

Cognitive Function Tests

The Mini-Mental State Examination (MMSE) [16], was devised as a screening test for possible dementia; it assesses orientation, registration, attention, calculation, language, and recall, with scores ranging from 0–30. The Trail-Making Test part B, from the Halstead-Reitan Neuropsychological Test Battery [17], tests visuomotor tracking and attention. The participant scans a page continuously to identify numbers and letters in a specified sequence while shifting from numbers to letter sets. A maximum of 300 seconds is given; scoring is the time taken to finish the test. A higher score indicates a poorer performance. Category fluency [18] is assessed by naming as many animals as possible in one minute. The score is the number of animals named correctly.

Laboratory analyses

Blood samples were collected in the morning and serum was separated and frozen at −70 C. The time between the last consumption of any food or drink and time of blood collection was recorded. IGF-1 and IGFBP-1 levels were measured using the Nichols Institute Diagnostics Commercial Kit (San Clemente, CA) modified to optimize sensitivity and specificity. Samples were diluted 1:105 and pretreated by acid-ethanol cryoprecipitation to remove IGF binding proteins. The assay sensitivity was 6.3 ng/ml; intra- and interassay coefficients of variation were 3.3% and 11.4%, respectively. IGFBP-1 levels were measured by an immunoradiometric assay kit (Diagnostics Systems Laboratories, Inc., Webster, TX) with a sensitivity of 0.33 ng/ml and intra- and interassay coeffecients of variation of 3.9% and 13.5% respectively.

Statistical Analyses

Data were analyzed using SPSS (version 15.0, SPSS, Inc., Chicago, IL). Descriptive analyses were conducted with analyses of covariance for continuous variables and Chi-square tests for categorical variables. IGFBP-1 was log transformed in the logistic regression analyses to minimize skewness. Multivariate logistic regression analyses was carried out to asses the association between IGF-1 and IGFBP-1 and dichotomous Trails B, Verbal Fluency and MMSE tests.

For categorical analyses, cut points for the cognitive function test scores were chosen based on established clinical values for normal and below normal performance on these tests. For Trails B, values less than 132 seconds were considered a good score; values of 132 seconds and more were not. For verbal fluency, those who had a score higher than 12 were considered good compared to those with a score of 12 or less. For MMSE, the scores above 24 were deemed good compared to those who had a score of 24 or less. In other analyses, we used the continuous cognitive function test results. Age and education were the only two significant covariates in the multivariate model. We also included estrogen use for women and time since last meal in the models. Because there was a sex interaction between IGF-1 levels and 2 of the 3 cognitive function tests, all the analyses were stratified by sex.

Results

There was a weak inverse correlation between IGF-I and IGFBP-1, which are biologically related ($r=-0.37$). IGF-1 mean ± (SD) levels among men were 98 ± (40.4) ng/ml and was 86.1 ± (38.5) among women. However, the IGF-1 range for women (8–443 ng/mL) was wider than the range for men (4–282 ng/mL). IGFBP-1 levels were comparable for both sexes. The lower 25 percentile for IGF-1 for men was less than 68 ng/mL and for women, it was 61 ng/mL.

There were more men (11.4%) in our study who performed worse in the MMSE score (i.e. scored less than 24) compared to women (5.8%) ($p<0.001$). In the Trails B, slightly more women (40.8%) performed worse (test score of >132 seconds) than men (35.3%) and the difference was statistically significant ($p=0.03$). There was no difference for verbal fluency test.

Table 1 presents the distribution of characteristics of the study populations with IGF-1 tertiles as the main exposure. All variables were significantly associated with IGF-1 tertiles except for exercise, education and alcohol intake. Those in the highest tertile of IGF-1 were younger and had a higher body mass index compared to those in lower tertiles. Men had higher IGF-1 levels than women, and women who used estrogen had lower IGF- levels compared to those who did not use it. All cognitive function tests were significantly related to IGF-1 levels, which is consistent with the assumption that lower IGF-1 levels are associated with poor cognitive function. Those in the lower IGF-1 tertile had lower MMSE and VF and higher Trails B scores (high Trails B indicates poorer cognitive function) than those in the highest IGF-1 tertile.

Table 2 presents logistic regression analyses using clinically-relevant cut points for each cognitive function test according to sex. IGFBP-1 was significantly inversely associated with higher VF score only among men (OR 0.39 95%CI 0.19–0.79). We then used the cognitive function tests as continuous outcome variables and categorized the IGF-1 into tertiles in a multivariate regression model adjusted for age, time since last meal, education, and estrogen use for models in women only (Table 3). In this analysis, verbal fluency was significantly associated with IGF-1 among men in a dose-response manner (P for trend = 0.01) where participants in both the middle and highest IGF-1 tertiles had better verbal fluency scores than those in the lowest tertile. Similarly, MMSE among the men was significantly associated with IGF-1 tertiles in a dose-response relationship (P for trend = 0.001). This was not the case for women, where none of the cognitive function tests were related to IGF-1. Including or excluding estrogen use by women in the model did not change the significance of the results. Similarly, including body mass index in any of the above models did not change the results.

For IGFBP-1, only the highest tertile was significantly different from the lowest tertile for the MMSE among men (Table 3). As expected, the association between IGFBP-1 and MMSE was inverse compared to the positive association of IGF-1 and MMSE. Similar to IGF-I, IGFBP-1 was not related to any cognitive function test among women.

Discussion

In this cohort study, IGF-I was independently associated with cognitive function among men but not among women. Higher IGF-1 levels were related to better cognitive test performance on verbal fluency and MMSE tests. For women, none of the cognitive function tests were related to IGF-1 levels. IGFBP-1 was inversely related to MMSE only in men comparing the highest with the lowest IGFBP-1. IGFBP-1 was also inversely related to a good verbal fluency score of 12 and above, only in men.

Our results support earlier findings that IGF-1 may have a role in neurodevelopment and cognitive function, especially in older age [1, 3]. Many of the previous studies on this association involved individuals with growth hormone (GH) deficiency leading to low GH and IGF-1 levels compared to most of the population. Our study included relatively healthy older individuals.

IGF-1 levels in our population for men and women were mostly in the normal range, but for both sexes, there was still approximately 25% who were lower than 60 ng/mL, which can be considered below the normal range mostly due to older age. This is reflected in Table 1, where the lowest IGF-1 tertiles had poor cognitive function and higher mean age.

The MMSE scores were positively correlated with IGF-1 levels similar to findings from smaller studies [9–11]. MMSE represents overall cognition, with low scores indicating cognitive impairment and possible dementia. This test is not used for specific areas of the central nervous system or cognition functions such as memory, fluid intelligence, information processing speed, executive cognition, spatial reasoning or verbal fluency. Kalmijn et al found that each SD increase of IGF-1 was associated with protection against decline in cognitive function (0.66 (0.45–0.97) after adjustment for all other covariates [11]. Dik et al. [19] failed to find a significant association between IGF-1 and MMSE, although there was a decline in MMSE with lower IGF-1 levels. They did not stratify associations by sex because the test for statistical interaction by sex was not significant. In an earlier report, Papadakis 1995 also failed to find an association between MMSE and IGF-1 levels in a small study of men aged 70 years and older [7]. Other studies have reported associations of specific components of cognition with IGF-1, but different cognitive function tests were used, which precludes a direct comparison with our results [6].

Trails B is a more specific cognitive function test and reflects visual and motor tracking and attention; it was not found significantly related to IGF-1 in our study. There are no studies reporting on Trails B among healthy men in relation to IGF-1. One growth hormone intervention [20] did show an improvement in Trails B score among elderly receiving growth hormone treatment compared to the placebo.

Verbal fluency performance and total IGF-1 levels were assessed in two studies from the Physicians' Health Study [13] and among women in the Nurses' Health Study [14]. There was a trend of improved verbal fluency with increasing IGF-1 tertiles for men, although this did not reach statistical significance in either sex from both studies, even after adjustment of other covariates of age, education, smoking, alcohol, body mass index, hypertension, and antidepressants. However, these two studies used telephone interviewing to determine verbal fluency and IGFBP-3 was analyzed and included it in the model to assess free IGF-1. Our results were related to total IGF-1 and this may explain why we did find a significant association with verbal fluency among men while the Physicians' Health Study did not.

Several trials have found evidence that supports an independent influence of IGF-1 on cognitive function. Papadakis [20] found no significant difference in MMSE in a trial comparing GH with placebo. GH regulates IGF-1 but, as shown by some interventions, IGF-1 can influence neural growth independent of GH [21]. Cherrier et al examined IGF-1, IGF-II, and four IGFBPs, as well as testosterone and estrogen in relation to verbal memory, divided attention, spatial memory, spatial ability and verbal fluency [12]. They found that increasing IGF-1 levels were associated with better verbal fluency among 25 elderly men independent of estradiol and testosterone.

The difference in sex in the relation between IGF-1 and cognitive function is interesting. The findings that men did not perform as well as women in the MMSE and that IGF-1 was related to MMSE only in men may be related to the importance of IGF-1 to cognitive function among individuals with lower than normal scores. However, this was not the case for Trails B, where women performed worse than men but there was no significant association with IGF-1 in either sex. Women in our study had lower IGF-1 mean levels than men but they had a wider range, and those who used estrogen had lower mean IGF-1 levels than those who did not. This is also supported by other studies showing oral estrogen use decrease IGF-1 levels [22, 23]. Some have found testosterone administration increases serum IGF-1 levels in men [24], and improve some cognitive functions, especially verbal fluency, among hypogonadal men [25]. The hormonal testosterone differences might not be the only explanation for the sex difference in our findings and further studies are needed for understanding the complex relationship between cognition and these hormones.

The mechanism by which IGF-I exerts its neuroprotective effects is not well understood. Some argue that IGF-I attenuates any damage from ischemia to the brain [26] by triggering hypoxia inducible factor-1 [27]. More commonly, IGF-I has been related to proliferation and antiapoptotic actions [28] leading to growth of oligodendrocytes, astrocytes, and microglia in the brain's white matter. Others have argued that IGF-I increases glucose uptake in brain tissue [29]. As IGF-I decreases with age because of the decrease in growth hormone secretion, IGF-I receptors in the brain also decrease with age [30]. Therefore, association between decline in IGF-1 and decline in cognitive function in older age is biologically plausible.

Limitations in our study include the lack of data on other IGF-1 binding proteins that would have allowed us to assess levels of free IGF-1 and the ratio of IGF-1 to its binding proteins. However, most prior studies used IGF-I levels rather than the binding proteins to study the association with cognitive function. Others have found positive association between IGF-1 and MMSE but not with free IGF-1 [11]. Although we included the potential confounders in the modeling of the association, these are not exhaustive; some studies adjusted for diet and mood variables, which were not available for our study. Blood samples were drawn in the morning but not from a fasting status of subjects, which is more likely to influence IGFBP-1 levels than IGF-1. We did adjust for time since the last meal. We may have underestimated associations because seniors with more severe cognitive decline would not have been able to provide consent or attempt the cognitive function tests. Our purpose was to see whether IGF-1 predicted mild cognitive impairment, not whether it was a marker for dementia.

In conclusion, we found an independent association of IGF-1 blood levels with two of three cognitive function tests in older men and no association in women. Additional studies are needed to replicate and attempt to explain these findings, which have potential implications for widespread use of growth hormone by older adults attempting to prevent or reverse consequences of aging.

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Abbreviations

IGF-1, Insulin-like growth factor-1; IGFBP-1, Insulin-like growth factor binding protein -1; MMSE, Mini-Mental State Exam; VF, Verbal Fluency; Trails B, Trail-Making Test part B; SD, standard deviation; SE, standard error; CI, confidence interval; GH, growth hormone.

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Table 1

Characteristics of the study population according IGF-1 tertiles

	Low tertile ≤72 N=521	***Middle tertile 73 – 105 N=506***	***High tertile ≥105 N=508***	**P value for trend**
	mean ± (SD)	mean ± (SD)	mean ± (SD)	
Mean IGF-1	51.1 ± (15.6)	88.4 ± (9.2)	134.8 ± (29.7)	
Mean Age (yrs)	74.9 ± (9.6)	72.2 ± (9.0)	71.5 ± (9.4)	<0.001
Mean body mass index	24.6 ± (3.9)	25.2 ± (3.6)	25.6 ± (3.7)	<0.001
Mean IFGBP1*	50.2 ± (36.8)	32.5 ± (25.3)	24.7 ± (22.3)	<0.001
Mean MiniMental State Exam (MMSE)	26.6 ± (3.1)	27.3 ± (2.1)	27.4 ± (1.9)	<0.001
Mean Trials B score	143.6 ± (72.7)	125.3 ± (58.9)	129.0 ± (63.9)	<0.001
Mean Verbal Fluency score	17.3 ± (5.2)	18.2 ± (5.1)	18.3 ± (4.9)	0.001
	%	**%**	**%**	
Female	65.3	60.9	49.4	<0.001
Exercise 3/days week	68.7	72.7	66.9	0.12
Estrogen use†				
Current	51.5	34.4	21.9	<0.001
Past	25.0	35.4	46.6	
Never	23.5	30.2	31.5	
Alcohol intake				
Abstainer	13.8	11.0	13.0	0.52
< 3/week	42.9	39.7	41.2	
≥ 3/week	43.4	49.2	45.8	
Education				
High school or less	32.3	31.0	32.2	0.89
Some college	29.1	32.7	31.2	
College graduate	24.7	24.0	22.2	
Graduate school	13.9	12.3	14.4	

*p value from log-transformed variable

†for women only

Table 2

Logistic regression models*, with IGF-1 and IGFBP-1 as independent variables and each cognitive function as a categorical dependent variable†

		Odds Ratio	*95% Confidence Interval*	P value
Men				
Mini Mental State Exam (MMSE) >24	IGF1	1.003	0.996–1.011	0.36
	IGFBP1	0.950	0.462–1.953	0.89
Verbal Fluency > 12	IGF1	1.005	0.998–1.023	0.14
	IGFBP1	0.385	0.188–0.789	0.009
Trails B < 132 seconds	IGF1	1.001	0.996–1.006	0.63
	IGFBP1	0.999	0.610–1.638	0.99
Women				
MMSE > 24	IGF1	0.997	0.988–1.006	0.51
	IGFBP1	0.406	0.149–1.109	0.08
Verbal Fluency > 12	IGF1	1.005	0.998–1.011	0.16
	IGFBP1	1.065	0.595–1.904	0.83
Trails B < 132 seconds	IGF1	0.999	0.994–1.003	0.646
	IGFBP1	1.021	0.676–1.545	0.92

*Adjusting for age, education and time since last meal Plus estrogen use for women

†Reference would be “good” cognitive function at baseline according to standard cut-points

Table 3

Beta coefficient, standard Error (SE) and p value for the effect of tertile of IGF-1 and IGFBP-1 on each of the cognitive function tests (lowest tertile is the reference) in the multivariate logistic regression.*

		Beta (SE)	*P value*	P trend
Men				
Mini Mental State Exam (MMSE)				
IGF1	middle	0.84 (0.27)	0.002	0.001
	high	0.92 (0.27)	0.001	
IGFBP1	middle	−.218 (0.25)	0.38	0.02
	high	−.665 (0.28)	0.017	
Verbal Fluency				
IGF1	middle	1.16 (0.51)	0.024	0.011
	high	1.27 (0.50)	0.011	
IGFBP1	middle	0.12 (0.46)	0.77	0.11
	high	−0.83 (0.52)	0.11	
Trails B				
IGF1	**middle**	−13.91 (5.6)	0.01	0.23
	high	−6.53 (5.4)	0.23	
IGFBP1	**middle**	−2.61 (4.94)	0.59	
	high	7.04 (5.64)	0.21	0.21
Women				
MMSE				
IGF1	middle	0.19 (0.16)	0.23	0.31
	high	0.17 (0.17)	0.31	
IGFBP1	middle	0.001 (0.17)	0.99	0.32
	high	−0.17 (0.17)	0.32	
Verbal Fluency				
IGF1	middle	0.002 (0.36)	0.99	0.19
	high	−0.50 (0.38)	0.19	
IGFBP1	middle	−0.24 (0.39)	0.54	0.95
	high	−0.02 (0.39)	0.95	
Trails B				
IGF1	**middle**	−3.01 (4.74)	0.53	0.38
	high	4.48 (5.06)	0.38	
IGFBP1	**middle**	−4.07 (2.17)	0.43	0.29
	high	5.44 (5.18)	0.29	

*Adjusted for age, time since last meal and education, and estrogen use for women.