Insulin-Like Growth Factor-1 Bioactivity Plays a Prosurvival Role in Older Participants

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The aim of this study was to address the intriguing issue of the role of the insulin-like growth factor (IGF)-1 system in longevity looking at the role of different components of IGF system. Vital status was ascertained in 1,197 men and women aged greater than or equal to 65 years from the InCHIANTI study. Hormonal levels were categorized into quartiles, and ratio of IGF-1 to IGF-binding protein (IGFBP)-1 was calculated. The relationship between hormones and mortality was tested by Cox proportional hazard models adjusted for age, sex, and confounders. During the 8-year follow-up period, 240 died and 957 survived. Lowest quartiles of IGF-1 and IGFBP-1 were considered as reference. Compared with the lowest quartiles, IGF-1 in upper quartiles was a negative predictor of mortality independent of age and sex (p = .01) but not independent of IGFBP-1 and other confounders. IGFBP-1 in second-third quartiles was negatively associated and that in the fourth quartiles was positively associated with risk of death. IGF-1/IGFBP-1 ratio in the lowest quartiles was a strong positive predictor of mortality, in age- and sex-adjusted model (p = .005), and independent of additional confounders (p = .037). High IGFBP-1 and low IGF-1/IGFBP-1 ratio are associated with all-cause mortality in older population.

Key Words: IGF-1 bioactivity—IGF-binding proteins—Mortality—Older participants.

Received January 13, 2013; Accepted March 25, 2013

Decision Editor: Rafael de Cabo, PhD

In many species, the insulin-like growth factor (IGF)-1 system exerts a complex role during specific stages of the life span. Insulin/IGF-1 signaling (IIS) pathway has been considered a potential determinant of longevity even though its role is still debated (1,2). In invertebrates, the disruption of the insulin/IGF-1 pathway increases life span, and the mutation of the homolog of insulin–IGF-1 receptor in invertebrates results in an attenuation of IIS, delayed aging, and extension of maximum life span (3). In mammals, the effects of decreased IGF-1 signaling remain controversial with mutations of genes involved in IIS pathway altering life span (4,5) and overexpression of muscle IGF-1 having antiaging impact on skeletal muscle growth and cachexia (6). The so-called IGF-1 enigma for life expectancy is also evident in humans where IGF-1 determines beneficial effects on skeletal muscle (1,7), vasculature, and metabolism (8,9) and also regulates the proliferation, differentiation and apoptosis, and is involved in the progression of cancer (10). By considering these two opposite mechanisms, it is not surprising that in older participants, low IGF-1 levels have been associated with cardiovascular and cerebrovascular diseases and mortality (11–14) and high IGF-1 levels have been related with cancer mortality (15,16). In addition, a U-shaped relationship has been found between IGF-1 and all-cause mortality (17).

A poor nutritional status, which is associated with low IGF-1 levels, could exacerbate the age-related decline in IGF-1 levels increasing the risk of death in older persons (18–21). IGF-1 bioactivity and bioavailability are also influenced by six binding proteins (IGF-binding proteins [IGFBPs]) that also exert independent biological actions (22,23). IGFBP-1 has stimulatory and inhibitory effects on IGF-1 bioactivity, with phosphorylated form of IGFBP-1 inhibiting IGF-1 system, whereas the unphosphorylated form has stimulatory effect.

Low IGFBP-1 levels may be found in obesity and other conditions of hyperinsulinemia, whereas IGFBP-1 levels increase with aging during stress and inflammatory conditions, starvation, muscle atrophy, hypoxia, and renal and liver diseases (24–32).
IGFBP-1 also affects mortality, through its IGF-dependent or -independent actions, including the ability to stimulate endothelium and vascular smooth muscle cells (2,22).

However, not all studies that have tested the predictive value of IGF-1 on mortality considered IGFBP-1, and most of the data on IGFBP-1 levels and mortality are conflicting.

IGFBP-1 levels have been shown as positive predictors of increased short- or long-term cardiovascular mortality in some studies (33–36), are inversely related with cardiovascular mortality in the Rancho Bernardo Study cohort (37), and are not significantly associated with cardiovascular mortality in others (38,39).

Because IGFBP-1 is also known to inhibit cancer cell growth and migration, it is not surprising that high IGFBP-1 levels result in higher risk of cancer mortality (40,41). Despite the tight regulation of IGF system, as well as the profound interaction of different components of IGF-1 system, the identification of a potential marker of whole system has not been adequately addressed. Studies investigating two possible indicators of IGF bioactivity, free IGF-1 (42) and IGF-1/IGFBP-3 molar ratio (43), have not produced convincing results (44). Therefore, in this study, we introduced a new potential indicator of IGF bioactivity, the IGF-1/IGFBP-1 ratio, and we have tested the relationship between IGF-1, IGFBP-1, IGFBP-3, IGF-1/IGFBP-3 molar ratio, and IGF-1/IGFBP-1 ratio with all-cause mortality and specific cause of mortality.

**Materials and Methods**

**Study Sample**

We analyzed 1,197 men and women aged more than 65 years from the InCHIANTI study, a large epidemiological study performed in Greve in Chianti and Bagno a Ripoli, two small towns of Tuscany, Italy. From the initial sample of 1,270 community-dwelling individuals aged more than 65 years of the InCHIANTI study, we selected 1,197 participants with complete data on IGF-1, IGFBP-1, and IGFBP-3. Participation rate was very high (91.6%). The Italian National Institute of Research and Care on Aging Institutional review board ratified the study protocol. Participants consented to participate and to have their blood samples analyzed for scientific purposes.

Eight-year vital status for the original InCHIANTI cohort was ascertained with data from the Tuscany Region Mortality General Registry maintained by the Registry Office of the Tuscany Region, including death certificates. The data collection was started in September 1998 and completed in March 2000. The characteristics of the study population have been described in detail elsewhere (45).

**Hormone Measurement**

Serum total IGF-1 and IGFBP-1 were measured at enrollment by immunoradiometric assay, using commercial reagents (Diagnostic Systems Laboratories). Inter- and intra-assay coefficients of variation for three different concentrations (low, medium, and high) were all less than 10%. The minimum detectable concentrations were 0.80 and 0.33 ng/mL for IGF-1 and IGFBP-1, respectively.

IGF-1/IGFBP-1 ratio was calculated. Serum interleukin-6 (IL-6) was measured in duplicate by high-sensitivity enzyme-linked immunosorbent assays (BioSource, Camarillo, CA). The minimum detectable concentration was 0.1 pg/mL, and the interassay coefficient of variation 4.5%.

Serum IGFBP-3 was measured by DSL-6600 ACTIVE Coated-Tube Immunoradiometric Assay kit. The minimum detection limit of IGFBP-3 is approximately 0.5 ng/mL. The intra- and interassay coefficients of variation were less than 4% and 2%, respectively.

IGF-1/IGFBP-3 molar ratio was also calculated. Plasma insulin level was determined with a double-antibody, solid-phase radioimmunoassay (intra-assay coefficient of variation = 3.1 + 0.3%; Sorin Biomedica, Milan, Italy). Cross-reactivity with human proinsulin was 0.3%.

**Comorbidity and Other Variables**

Physical activity in the year before the interview was coded as (a) sedentary if participants are completely inactive or if they have light-intensity activity less than 1 hour per week; (b) light if they have light-intensity activity 2–4 hours per week; and (c) moderate to high if they have light activity at least 5 hours per week or more or moderate activity at least 1–2 hours per week. Daily total energy intake (kcal) was estimated by the European Prospective Investigation into Cancer and Nutrition food frequency questionnaire.

Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared. Diseases were assessed by experienced physician according to pre-established criteria that combine self-reported history, physician diagnoses, current pharmacologic treatment, medical records, clinical examinations, and blood tests. Diseases included in the current analysis were congestive heart failure (CHF) and ischemic stroke.

Mortality General Registry maintained by the Tuscany Region and the death certificates that are deposited immediately after the death at the Registry office of the Municipality of residence.

**Statistical Analysis**

Variables are reported as mean ± standard deviation, median and interquartile range, or numbers and percentages. Because of skewed distributions, log-transformed values of total IGF-1, IL-6, IGFBP-1, and IGFBP-3 were used in regression analyses.

Cox proportional hazard models adjusted for age, sex, caloric intake, GOT, fasting insulin, BMI, dehydroepiandrosterone sulfate (DHEAS), testosterone, IL-6, CHF, stroke, and physical activity were used to assess the effects of baseline values of IGF-1, IGFBP-1, IGF-1/IGFBP-1 ratio, IGFBP-3, and IGF-1/IGFBP-3 molar ratio on all-cause mortality and specific causes of mortality.
Covariates were included in the multivariate models if they were statistically associated with mortality in univariate analysis. All analyses were performed with the SAS statistical package, version 9.1 (SAS Institute Inc, Cary, NC).

**Results**

A total of 240 participants died and 957 survived during the 8-year follow-up period. Participants who died were significantly older, and more likely to be men and more sedentary, and having higher GPT, IL-6 levels, and higher prevalence of CHF and ischemic stroke. Moreover, participants who died had significantly lower IGF-1, IGFBP-3, and DHEAS levels than survivors at baseline (Table 1).

**Insulin-Like Growth Factor-1**

As expected, IGF-1 levels were negatively associated with age. As shown in Table 2, in the model adjusted for age and gender, low IGF-1 levels were predictors of higher all-cause mortality (hazard ratio [HR] 0.62 CI: 0.43–0.89, *p* = .01). Participants were categorized according to quartiles of IGF-1 levels. IGF-1 levels in the first quartile were less than 76.78 ng/mL, the second quartile greater than 76.78 and less than 109 ng/mL, and the third quartile greater than 109 and less than 140.9 ng/mL. The highest quartile includes participants with IGF-1 levels greater than 140.9 ng/mL.

After adjustment for age, sex, caloric intake, GOT, fasting insulin, BMI, DHEAS, testosterone, IL-6, CHF, stroke, physical activity, and IGFBP-1, the inverse relationship between IGF-1 and mortality was no longer significant (HR 0.66 CI: 0.24–1.83, *p* = .44).

**Insulin-Like Growth Factor-Binding Protein-1**

As expected, we found a positive association between IGFBP-1 and age (Figure 1). The participants were also categorized according to the IGFBP-1 levels: first quartile less than 18.13 ng/mL, second quartile between 18.13 and 29.31 ng/mL, third quartile between 29.31 and 44.15 ng/mL, and the fourth quartile including participants with IGFBP-1 levels higher than 44.15 ng/mL.

As shown in Table 3, higher IGFBP-1 levels were significant predictors of death in age- and sex-adjusted analyses (HR 1.012 CI: 1.000–1.017, *p* < .001). After further adjustment for confounders including IGF-1, the relationship between IGFBP-1 levels and mortality was still significant (HR 1.010 CI: 1.004–1.017, *p* = .003).

**IGF-1/IGFBP-1 Ratio**

As a consequence of the decline in IGF-1 levels and the increase in IGFBP-1, the IGF-1/IGFBP-1 ratio decreased with age (Figure 2). In the age- and gender-adjusted model, low IGF-1/IGFBP-1 ratio is a positive predictor of all cause of mortality (HR 0.556 CI: 0.368–0.840, *p* = .0053). Low IGF-1/IGFBP-1 ratio was still a significant predictor of death in the multivariate model adjusted for BMI, fasting insulin, IL-6, testosterone, DHEAS, physical activity, and chronic diseases (HR 0.590 CI: 0.360–0.968, *p* = .037) (Table 4), and the relationship between IGF-1/IGFBP-1 ratio and all-cause mortality remained still significant after adjustment for IGFBP-3 (HR 0.53 CI: 0.36–0.97, *p* = .04).

**IGFBP-3 and IGF-1/IGFBP-3 Molar Ratio**

The participants were categorized according to the IGFBP-3 and IGF-1/IGFBP-3 molar ratio levels (Table 5). IGFBP-3 in third and fourth quartiles were significant

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**Table 1. Characteristics of Study Population (N = 1,197) According to Vital Status**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Survivors (n = 957)</th>
<th>Died (n = 240)</th>
<th><em>p</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>66.8 ± 15.6</td>
<td>81.9 ± 7.8</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Gender (female %)</td>
<td>660 (56.8)</td>
<td>85 (46.7)</td>
<td>.01</td>
</tr>
<tr>
<td>IGF-1 (ng/mL)</td>
<td>28.3 ± 19.1</td>
<td>46.8 ± 31.0</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>IGFBP-3 (ng/mL)</td>
<td>44.2 ± 10.7</td>
<td>37.8 ± 12.1</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Total IGF-1 (ng/mL)</td>
<td>133.5 ± 67.0</td>
<td>99.8 ± 53.8</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>GOT (U/L)</td>
<td>21.3 ± 8.9</td>
<td>20.6 ± 10.8</td>
<td>.39</td>
</tr>
<tr>
<td>GPT (U/L)</td>
<td>20.7 ± 13.3</td>
<td>17.2 ± 13.5</td>
<td>.01</td>
</tr>
<tr>
<td>Fasting insulin (mIU/L)</td>
<td>10.8 ± 6.3</td>
<td>10.1 ± 5.6</td>
<td>.09</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>27.2 ± 4.2</td>
<td>26.8 ± 3.7</td>
<td>.26</td>
</tr>
<tr>
<td>Dehydroepiandrosterone sulfate (µg/dL)</td>
<td>111.7 ± 99.7</td>
<td>71.6 ± 66.0</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Testosterone (ng/mL)</td>
<td>2.3 ± 2.1</td>
<td>2.4 ± 1.9</td>
<td>.48</td>
</tr>
<tr>
<td>Interleukin-6 (pg/mL)</td>
<td>1.8 ± 3.1</td>
<td>3.6 ± 7.1</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Stroke, n (%)</td>
<td>39 (3.4)</td>
<td>21 (11.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>122 (16.5)</td>
<td>63 (30.1)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Congestive heart failure, n (%)</td>
<td>158 (13.6)</td>
<td>95 (52.2)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Notes. The values are expressed as M ± SD or numbers (n) and percent-age (%). IGFBP = insulin-like growth factor-binding protein; GPT = Glutamyl pyruvic transaminase; GOT = Glutamyl oxaloacetic transaminase.

**Table 2. Multivariate Analysis Testing the Relationship Between IGF-1 With All-Cause Mortality in Older Adults**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>HR 95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IGF-1 first quartile (&lt;76.78 ng/mL)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>IGF-1 second quartile (76.78–109 ng/mL)</td>
<td>0.67</td>
<td>0.51–0.88</td>
</tr>
<tr>
<td>IGF-1 third quartile (109–140.9 ng/mL)</td>
<td>0.69</td>
<td>0.51–0.94</td>
</tr>
<tr>
<td>IGF-1 fourth quartile (&gt;140.9 ng/mL)</td>
<td>0.62</td>
<td>0.43–0.89</td>
</tr>
<tr>
<td>Model 2†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IGF-1 first quartile (&lt;76.78 ng/mL)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>IGF-1 second quartile (76.78–109 ng/mL)</td>
<td>0.78</td>
<td>0.50–1.21</td>
</tr>
<tr>
<td>IGF-1 third quartile (109–140.9 ng/mL)</td>
<td>0.79</td>
<td>0.42–1.44</td>
</tr>
<tr>
<td>IGF-1 fourth quartile (&gt;140.9 ng/mL)</td>
<td>0.66</td>
<td>0.24–1.83</td>
</tr>
</tbody>
</table>

Notes. IGF = insulin-like growth factor.

*Model 1: Adjusted for age and sex.
†Model 2: Adjusted for age, sex, caloric intake, GOT, fasting insulin, body mass index, dehydroepiandrosterone sulfate, testosterone, interleukin-6, congestive heart failure, stroke, physical activity, and IGFBP-1.
IGF-1, IGFBP-1, AND MORTALITY IN ELDERLY PARTICIPANTS

predictors of death in age- and sex-adjusted analyses (HR 0.69 CI: 0.52–0.93, p = .01) (HR 1.43 CI: 1.03–1.98, p = .03). After further adjustment for confounders, the relationship between IGFBP-3 levels and mortality remained still significant only for IGFBP-3 in the third quartile (HR 0.66 CI: 0.47–0.93, p = .01). In the Cox hazard model analysis testing the relationship between IGF-1/IGFBP-3 molar ratio and mortality, we found no significant relationship between IGF-1/IGFBP-3 molar ratio and risk of all-cause mortality in both age- and sex-adjusted model and fully adjusted model (Table 6).

Cardiovascular Mortality

Of the 240 participants, 72 died for cardiovascular disease (stroke, myocardial infarction, and CHF) during the 8-year follow-up period. The relationship between the single components of IGF axis and the cardiovascular mortality was examined. In age- and gender-adjusted model, no significant relationship was found between cardiovascular mortality, IGF-1 (p = .78), and IGF-1/IGFBP-1 ratio (p = .85). Although IGFBP-1 levels were positively associated with cardiovascular mortality (p = .08), the relationship was no longer significant after adjustment for other confounders. No significant effect was also found for IGFBP-3 and IGF-1/IGFBP-3 molar ratio and cardiovascular mortality (data not shown).

Discussion

Hormonal Changes During Aging

As expected, our findings suggest that aging is accompanied by quantitative changes in plasma levels of components of IGF axis. Consistent with other studies, we observed a negative relationship between IGF-1 levels and age (46,47) and a positive relationship between IGFBP-1 levels and age confirming the data from Rutkute and coworkers (48) and Rutanen and coworkers (49).

The IGF-1 decline during aging reflects many changes occurring at hypothalamic, pituitary, and tissue levels. The age-related increase in IGFBP-1 levels can be exacerbated by coexistent chronic diseases, such as renal or liver failure,
hypoxia, inflammatory states, malnutrition and muscle atrophy, and conditions highly frequent in older populations (24–32).

Our study also showed an inverse relationship between IGF-1/IGFBP-1 ratio and age, suggesting an imbalance between IGF-1 and IGFBP-1 during the aging process and its usefulness as reliable marker of IGF-1 bioactivity.

**IGF-1 and All-Cause Mortality**

We found a negative relationship between IGF-1 levels and all-cause mortality independent of age and sex. This result is consistent with previous studies (37,50), suggesting a potential and protective role for IGF-1 in the development of disability and mortality.

IGF-1 exerts a potential protective role in cardiovascular system by different mechanisms. They include the stimulation of nitric oxide (NO) synthase and vasodilation, the increase in peripheral glucose uptake, decreased gluconeogenesis, antiplatelet effects, and the scavenging of oxygen-free radicals (51,52).

In addition to these protective effects on vascular system, IGF-1 has been shown to increase the recruitment of
IGFBP-1, IGF-1, AND MORTALITY IN ELDERLY PARTICIPANTS

Table 6. Multivariate Analysis Testing the Relationship Between IGF–1/IGFBP-3 Molar Ratio With All-Cause Mortality in Older Adults

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>HR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IGF-1/IGFBP-3 MR first quartile</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>IGF-1/IGFBP-3 MR second quartile</td>
<td>0.73</td>
<td>0.74–0.55</td>
<td>0.98</td>
</tr>
<tr>
<td>IGF-1/IGFBP-3 MR third quartile</td>
<td>0.93</td>
<td>0.69–1.25</td>
<td>0.63</td>
</tr>
<tr>
<td>IGF-1/IGFBP-3 MR fourth quartile</td>
<td>0.96</td>
<td>0.72–1.29</td>
<td>0.80</td>
</tr>
<tr>
<td>Model 2†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IGF-1/IGFBP-3 MR first quartile</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>IGF-1/IGFBP-3 MR second quartile</td>
<td>0.82</td>
<td>0.59–1.13</td>
<td>0.22</td>
</tr>
<tr>
<td>IGF-1/IGFBP-3 MR third quartile</td>
<td>0.95</td>
<td>0.69–1.33</td>
<td>0.77</td>
</tr>
<tr>
<td>IGF-1/IGFBP-3 MR fourth quartile</td>
<td>0.98</td>
<td>0.70–1.36</td>
<td>0.89</td>
</tr>
</tbody>
</table>

Notes. IGF = insulin-like growth factor; IGFBP = IGF-binding protein.
*Model 1: Adjusted for age and sex.
†Model 2: Adjusted for age, sex, caloric intake, GOT, fasting insulin, body mass index, dehydroepiandrosterone sulfate, testosterone, interleukin-6, congestive heart failure, stroke, and physical activity.

There are other beneficial actions of IGF-1 on skeletal muscle mass, immune system, central nervous system, and body composition that can explain why this anabolic hormone may exert a protective role on longevity (56–59).

In our study, the relationship between IGF-1 and mortality was no longer significant after adjustment for multiple confounders, including testosterone, DHEAS, fasting insulin, and IGFBP-1.

The loss of significance suggests that the protective role of IGF-1 is just a part of a complex landscape of anabolic hormonal changes during aging.

We previously reported in the older male population of InCHIANTI study that the simultaneous presence of multiple anabolic hormone deficiencies (testosterone, DHEAS, and IGF-1) with subsequent endocrine imbalance toward catabolism is a better predictor of mortality than a single hormonal impairment (59).

IGFBP-1 and All-Cause Mortality

Our study also showed a positive relationship between IGFBP-1 levels and all-cause mortality. This effect was independent of several confounders, including IGF-1 and fasting insulin, the main regulator of the hepatic production of IGFBP-1.

These findings are consistent with other studies conducted in adult older participants, showing a positive relationship between IGFBP-1 levels, cardiovascular mortality (34–36,60–63), and cancer.

However, data from Rancho Bernardo Study showed a protective, rather than permissive role of high IGFBP-1 levels on cardiovascular mortality. The reason of this discrepancy is unclear, but it is possible to hypothesize a U-shaped relationship between IGFBP-1 and mortality. If this hypothesis is true, both low IGFBP-1 levels, commonly associated with obesity and hyperinsulinemia, and high IGFBP-1 levels, commonly observed during malnutrition, inflammation, and stress (25–27), are predictors of poor outcomes in older patients. In this scenario, only intermediate values of IGFBP-1 would be protective for mortality.

Therefore, the increased mortality for low IGFBP-1 concentrations observed by Laughlin and coworkers (37) could be related to a less favorable cardiovascular profile, namely higher lipoproteins and blood pressure. Conversely, the increased mortality associated with high IGFBP-1 found in our study may be due to the inhibition of the IGF-1 axis. Our findings are consistent with another recent analysis conducted in cardiovascular health study all stars study where increasing IGFBP-1, but not IGF-1, was a significant predictor of increased risk of mortality (63). These conflicting results require the need of future studies and explain why we looked at more reliable indexes of IGF bioactivity.

IGF-1/IGFBP-1 Ratio and All-Cause Mortality

IGF-1/IGFBP-1 ratio might be a new reliable index of the IGF bioactivity, being the IGFBP-1, the main modulator of the action of IGF-1. Moreover, this ratio takes into account the dysregulation of both components, namely the decline of IGF-1 and the increase in IGFBP-1 that occurs with aging and is accentuated during stress, inflammation, malnutrition, and liver and renal diseases.

Our study showed that the participants with IGF-1/IGFBP-1 ratio in the lower quartile had a worse survival curve, compared with those with IGF-1/IGFBP-1 ratio in the upper quartile. This positive association remained significant after adjustment for multiple confounders, including fasting insulin, caloric intake, physical activity, liver function, IL-6, testosterone, and DHEAS.

The relationship was also independent of IGFBP-3, which is the storage protein for IGF-1 and has also independent actions on outcomes other than survival. Because many researchers in the aging field have learnt about the role of IGF-1 in aging solely from studies conducted in invertebrates, our results provide further strength on the antiaging role of IGF-1 bioactivity in humans.

Moreover, no significant relationship was found for IGFBP-3 and more importantly and IGF/IGFBP-3 molar ratio and all-cause mortality. These data together suggest that the IGF/IGFBP-1 ratio probably represents a more reliable marker of IGF-1 bioactivity and a more powerful indicator of adverse outcomes than IGF-1 and IGFBP-1, considered separately, and other indexes of IGF bioactivity in older participants.
IGF-1/IGFBP-1 Ratio and Cardiovascular Mortality

We failed to find a significant relationship between IGF-1/IGFBP-1 ratio and cardiovascular mortality. However, due to limited number of cardiovascular deaths, we cannot completely reject the hypothesis that low IGF bioactivity affects the development and progression of cardiovascular diseases. It cannot be excluded that low IGF bioactivity may be an epiphenomenon of a poor health status rather than a determinant of all-cause mortality. Because all the components of the IGF axis are affected by several conditions, including inflammation and nutritional status, in our study, we have adjusted for BMI, caloric intake, fasting insulin, and IL-6, but the strength of our results was unaffected.

Limitations

The study has some limitations. First, the hormonal measurement was performed at the enrollment, but we do not have additional information during the follow-up. Because many conditions may have an impact on IGF axis, we cannot exclude the fact that residual confounders not considered in the present analysis may have affected our results.

Finally, we do not have information regarding the IGF receptors, an important component of the axis and IGFBPs other than IGFBP-1 and IGFBP-3. Therefore, we acknowledge that this information would have made much stronger the manuscript by giving a more complete overview of IGF system.

Strengths

The limitations are offset by important strengths. The response rate of population was high (>90%). The study included a relatively high number of participants (1,197) with a remarkable number of confounders, which are not easily found in other epidemiological studies. We tried to consider the entire IGF-1 axis, including different components of the system, IGF-1, IGFBP-1, and IGFBP-3, and identified a new potential index of IGF bioactivity, the IGF-1/IGFBP-1 ratio.

Conclusions

Our study shows that IGF-1 alone is not a good predictor of survival in the elderly participants. The IGFBP-1 levels are positively associated and IGF-1/IGFBP-1 ratio is negatively associated with all-cause mortality, suggesting a strong link between IGF-1 bioactivity and survival in the elderly participants.

Funding

The InCHIANTI study was supported as a “targeted project” (ICS 110.1/RS97.71) by the Italian Ministry of Health, the U.S. National Institute on Aging (contracts N01-AG-916413 and N01-AG-821336), in part, the Intramural Research Program of the U.S. National Institute on Aging (contracts 263 MD 916413 and 263 MD 821336), and grant RF-2010-2312659 from the Italian Ministry of Health and Emilia Romagna Region. None of the sponsoring institutions interfered with the collection, analysis, presentation, or interpretation of the data reported here.

Acknowledgments

We thank Fabrizio Ablondi, Maurizio Conca, and Pietro Schianchi for their technical support.

Conflict of Interest

The authors declare that they have no conflict of interest to disclose concerning this manuscript.

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