Body mass index, free insulin-like growth factor I, and physical function among older adults: results from the ilSIRENTE study

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Submitted 22 March 2006; accepted in final form 19 April 2006

Onder, Graziano, Rosa Liperoti, Andrea Russo, Manuel Soldato, Ettore Capoluongo, Stefano Volpato, Matteo Cesari, Franco Ameglio, Roberto Bernabei, and Francesco Landi. Body mass index, free insulin-like growth factor I, and physical function among older adults: results from the ilSIRENTE study. *Am J Physiol Endocrinol Metab* 291: E829–E834, 2006; doi:10.1152/ajpendo.00138.2006.—The aim of the present study was to evaluate the mediating role played by obesity on the relationship of free insulin-like growth factor I (IGF-I) and IGF-binding protein-3 (IGFBP-3) with muscle strength and physical performance. Data were from baseline evaluation of the ilSIRENTE Study. Muscle strength was measured by hand grip strength. Physical performance was assessed using the walking speed and the 0–3 Short Physical Performance Battery (SPPB) score. Based on its median value, free IGF-I was categorized in the following two groups: low IGF-I (IGF-I <0.65 ng/ml; n = 174) and high IGF-I (IGF-I ≥0.65 ng/ml; n = 175). Similarly, IGFBP-3 was categorized in the following two groups: low IGFBP-3 (IGFBP-3 <4.319.9 ng/ml; n = 174) and high IGFBP-3 (IGFBP-3 ≥4.319.9 ng/ml; n = 175). Body mass index (BMI) was categorized as follows: <25 kg/m² (n = 160), 25–29.9 kg/m² (n = 133), ≥30 kg/m² (n = 56). Mean age of the 349 participants was 85.8 yr, and 234 (67%) were women. After adjusting for potential confounders, no significant association of IGF-I and IGFBP-3 with study outcomes was observed. After the study sample was stratified by BMI groups, compared with participants with low IGF-I level, those with high IGF-I level had a significantly bigger grip strength [35.2 ± 1.6 vs. 29.2 ± 2.0 (SE) kg, P = 0.03], walking speed (0.55 ± 0.04 vs. 0.40 ± 0.04 m/s, P = 0.01), and SPPB score (1.9 ± 0.1 vs. 1.5 ± 0.1 m/s, P = 0.01) but only in the group with BMI ≥30 kg/m² and not in other BMI groups. A statistically significant interaction between BMI and IGF-I level was observed on all study outcomes. By contrast, no association was observed between IGFBP-3 and study outcomes, independently of BMI. In conclusion, high IGF-I level is associated with better physical function in older persons with obesity, but not in nonobese subjects.

insulin-like growth factor I; physical performance; muscle strength; older adults; obesity

AGE-RELATED DISABILITY AND LOSS in physical function are growing public health priorities (14). Loss in physical function seriously threatens the independence and quality of life of older adults and has a significant social and economic impact on our society (10). Older people who lose the ability to complete basic tasks of daily living are less likely to remain in the community, have higher rates of morbidity and mortality, and have more hospitalizations and a poorer quality of life (36). Therefore, identification of mechanism involved in maintenance of physical function and prevention of functional decline in older persons represents one of the primary goals of geriatric medicine.

Alterations in the hormonal axes have been proposed as critical, independent mediators of functional decline in older adults. In particular, insulin-like growth factor I (IGF-I) has been indicated as an important modulator of muscle strength and function, not only during the developmental period but across the entire life span (2, 24). Although biological plausibility supports a role in the disablment process, studies assessing the association of IGF-I and IGFBP-3 with muscle strength and physical performance in older adults have provided conflicting results (3, 5, 16, 18).

Despite controversial results reported for the relationship between obesity and IGF-I, an association between these two factors is reasonable because obesity can affect growth hormone (GH) secretions, which represents the primary determinant of IGF-I production (21, 33). Interestingly, in obese subjects, a number of trials have demonstrated that treatment with GH or IGF-I is effective in reducing fat mass, in sustaining lean body mass, and improving insulin sensitivity (9, 17, 35). These effects may, in turn, have an impact in physical function. However, so far, no study has examined if the association of IGF-I and IGFBP-3 with physical function differs between obese and nonobese subjects. Therefore, the aim of the present study was to evaluate the relationship of IGF-I and IGFBP-3 with muscle strength and physical performance measure according to body mass index (BMI).

METHODS

The ilSIRENTE study is a prospective cohort study performed in the mountain community living in the Sirente geographic area (L’Aquila, Abruzzo) in Central Italy. This study was designed by the Department of Gerontology of the Catholic University of Sacred Heart (Rome, Italy) and developed by the teaching nursing home Opera Santa Maria della Pace (Fontecchio, L’Aquila, Italy) in a partnership with local administrators and primary care physicians of Sirente Mountain Community Municipalities. All the participants signed an informed consent at the baseline visit. Details of the ilSIRENTE study protocol are described elsewhere (19).

Briefly, a preliminary list of all community-dwelling older adults living in the Sirente area was obtained at the end of October 2003 from the Registry Offices of the 13 municipalities involved in the...
study. From this preliminary list, potential study participants were identified by selecting all persons born before January 1, 1924 living in the Sirente area. Of the initial 514 subjects screened, 32 men and 53 women died or moved away from the area before the baseline assessment. Among those eligible (n = 429), prevalence of refusals was 16%. Subjects participating to the study did not differ significantly from those who refused to participate by age and sex. As a result, the overall sample population enrolled in the iISIRENTE study consisted of 364 subjects.

Data Collection

Baseline participants’ assessments began in December 2003 and were completed in September 2004. Assessors were trained on how to perform each component of the iISIRENTE study protocol. The Minimum Data Set for Home Care (MDS-HC) form was administered to all study participants, following the guidelines published in the MDS-HC manual (22, 23). The MDS-HC contains over 350 data elements, including sociodemographics, physical and cognitive status variables, and major clinical diagnoses (22). The MDS-HC also includes information about an extensive array of signs, symptoms, syndromes, and treatments (22).

Clinical diagnoses were recorded by study physicians gathering information from the patient; the general practitioner; after physical examination, careful review of patient clinical documentation (including laboratory tests and X-rays); and based on previous medical history. The cognitive performance scale (CPS) was used to assess cognitive status (15). The CPS has shown an excellent interrater and test-retest reliability when completed by nurses performing usual assessment duties (15, 20). The CPS score ranges from zero (intact cognition) to six (severe dementia). The depression rating scale was used to assess the presence of depressive symptoms (4). Based on a previous observation, participants with a score greater than or equal to three were diagnosed as depressed (4). Participants reporting light-intensity (aerobic) exercise performed for at least 2–4 h/wk during the last year were defined physically active. Drugs were coded according to the Anatomical Therapeutic and Chemical Codes (28). BMI was defined as weight (kg) divided by the square of height (meters). For analytical purpose, the study sample was divided in the following three groups according to BMI: <25 kg/m², 25–29.9 kg/m², and ≥30 kg/m².

Blood Measurements

Approximately 97% of participants consented to phlebotomy in the home, performed by a trained phlebotomist who followed a standardized protocol. The blood samples were immediately centrifuged and stored at −80°C until final analysis.

IGF assay. Free IGF-I and IGFBP-3 in blood were measured in triplicate by the RIA method (Diagnostic Systems Laboratories, commercialized in Italy by Puntec, Turin, Italy). Standard determinations of serum glucose, albumin, cholesterol, lactate dehydrogenase, and amylasemia were performed by commercially available kits (Olympus) suitable on Olympus 2700 instrumentation. C-reactive protein was measured by a high-sensitivity ELISA kit (Bender MedSystems). Outcome Measures

Muscle strength measure. Grip strength was used as an indicator of muscle strength. Grip strength is known to be positively correlated with lower-extremity strength and performance in older persons, and this measure has shown to be predictive of major health-related events in older persons (1, 31). Moreover, grip strength is a reliable test that can be easily administered in a home setting (1). Grip strength was assessed by hand grip strength measured by a dynamometer. One trial on each hand was done. The result of the stronger hand was used in the analyses.

Walking speed. Walking speed was evaluated by having the participant walk at his/her usual pace over a 4-meter course. A single walk was performed. This measure has been shown to be predictive of the onset of incident disability, mortality, and nursing home and hospital admission in older participants (13, 29). Moreover, this test has shown a high test-retest reliability (12).

Physical performance battery. Physical performance was assessed using standardized measures conducted by trained examiners. These included the 4-meter walking speed, the chair stands, and the balance tests. Individual measures of these tests were rescaled to values ranging from 0 (worst performance) to 1 (best performance), as previously described (27). The sum of the results from the three rescaled tests was used in the present study to calculate the Short Physical Performance Battery (SPPB) score. In previous studies, this measure has shown to be a valid and reproducible measure that can discriminate small and clinically meaningful differences in physical function and to be predictive of different forms of disability among older adults (25, 26).

Statistical Analysis

For the present study, from the initial sample of 364 participants, we excluded five participants because data on BMI was not collected and 11 because IGF-I and IGFBP-3 were not determined. This selection resulted in a final sample size of 349 participants. For analytical purposes, the following two groups of free IGF-I were created based on the median value of this variable: low IGF-I (IGF-I <0.65 ng/ml; n = 174) and high IGF-I (IGF-I ≥ 0.65 ng/ml; n = 175). Similarly, the following two groups of IGFBP-3 were created based on the median value of this variable: low IGFBP-3 (IGFBP-3 <4,319.9 ng/ml; n = 174) and high IGFBP-3 (IGFBP-3 ≥4,319.9 ng/ml; n = 175).

Baseline characteristics of the study sample across BMI groups were compared using ANOVA analyses for normally distributed variables, nonparametric Kruskal-Wallis H tests for skewed variables, and χ² analyses for dichotomous variables.

Analysis of covariance was used to compare adjusted means of hand grip strength, walking speed, and SPPB between IGF-I and IGFBP-3 groups. Because we hypothesized that BMI could modify the association of IGF-I and IGFBP-3 on study outcomes, we repeated the analysis separately in each BMI group and we formally tested the interaction of IGF-I and IGFBP-3 levels by introducing interaction terms in the fully adjusted models. Variables considered for adjustment were those associated with BMI at P ≤ 0.10 at the univariate analysis and those thought to be clinically significant. Final analyses were adjusted for age, gender, CPS score, physical activity, number of diseases, osteoarthritis, ischemic heart disease, cancer, diabetes, serum low-density lipoprotein (LDL), and C-reactive protein. For these analyses, to ensure normal distribution, C-reactive protein was log-transformed.

All analyses were performed using SPSS software (version 10.1, SPSS, Chicago, IL).

RESULTS

The mean age of the 349 participants was 85.8 yr (SD 4.8); 234 (67%) were women; and 160 (45.8%) had a BMI <25 kg/m², 133 (38.1%) between 25 and 29.9 kg/m², and 56 (16%) ≥30 kg/m². In this study sample, free IGF-I values ranged from 0.01 to 4.24 ng/ml [median 0.65, interquartile range (IQR) 0.40–1.08] and IGFBP-3 from 1.198 to 9.921 ng/ml [median 4.320, IQR 3.445–5.389]. The distribution of demographic, functional, clinical, and biochemical characteristics according to BMI groups is presented in Table 1. Free IGF-I and IGFBP-3 did not differ significantly across BMI groups. Overall, participants with BMI ≥30 kg/m² were younger, more likely female, had a higher number of comorbid conditions, a higher prevalence of ischemic heart disease, and more elevated
levels of LDL cholesterol. Across BMI groups, significant
differences were observed for grip strength (mean ± SE: BMI
<25 kg/m², 30.0 ± 1.0 kg; BMI 25–29.9 kg/m², 34.3 ± 1.3 kg;
BMI ≥30 kg/m², 32.8 ± 1.6, P = 0.02) and SPPB (BMI <25
kg/m², 1.5 ± 0.1 kg; BMI 25–29.9 kg/m², 1.7 ± 0.1 kg; BMI
≥30 kg/m², 1.7 ± 0.1 kg, P = 0.05) but not for walking speed
(BMI <25 kg/m², 0.48 ± 0.03 kg; BMI 25–29.9 kg/m², 0.51 ±
0.02 kg; BMI ≥30 kg/m², 0.47 ± 0.04 kg, P = 0.63).

In the overall sample, at the univariate analyses, IGF-I levels
were not significantly associated with any of the study out-
comes (grip strength, mean ± SE: low IGF-I 30.8 ± 1.0 kg,
high IGF-I 33.4 ± 1.1 kg, P = 0.08; walking speed: low IGF-I
0.49 ± 0.02 m/s, high IGF-I 0.49 ± 0.02 m/s, P = 0.87; SPPB
score: low IGF-I 1.6 ± 0.1, high IGF-I 1.7 ± 0.1, P = 0.35).
After adjusting for potential confounders, which included age,
gender, CPS score, physical activity, number of diseases,
osteoarthritis, ischemic heart disease, cancer, diabetes, serum
LDL, and C-reactive protein (log value), a borderline sig-
nificant association was observed between IGF-I levels and grip
strength (low IGF-I 31.3 ± 0.8 kg, high IGF-I 33.5 ± 0.8 kg,
P = 0.06), but no significant association was found with SPPB
score and walking speed.

At the univariate analyses, participants with high IGFBP-3
level tended to have better grip strength, SPPB score, and
walking speed compared with those with low IGFBP-3 level
(grip strength, low IGFBP-3 30.6 ± 1.1 kg, high IGFBP-3
33.6 ± 1.0 kg, P = 0.04; SPPB score: low IGFBP-3 1.5 ± 0.1
kg, high IGFBP-3 1.7 ± 0.1 kg, P = 0.05; walking speed: low
IGFBP-3 0.46 ± 0.02 m/s, high IGFBP-3 0.52 ± 0.02 m/s,
P = 0.06). However, the association of IGFBP-3 levels with
SPPB score and walking speed did not hold in the fully
adjusted model, and only the association between IGFBP-3
levels and grip strength reached a borderline statistical signif-
cance (low IGFBP-3 31.3 ± 0.8 kg, high IGFBP-3 33.4 ± 0.8
kg, P = 0.08).

As shown in Tables 2–4, after the study sample was strati-
fied by BMI groups, in the fully adjusted model, compared
with participants with low IGF-I level, those with high IGF-I
level had significantly better results in grip strength (35.2 ± 1.6
vs. 29.2 ± 2.0 kg, P = 0.03), walking speed (0.55 ± 0.04 vs.
0.40 ± 0.04 m/s, P = 0.01), and SPPB score (1.9 ± 0.1 vs.
1.5 ± 0.1 m/s, P = 0.01) but only in the group with BMI ≥30
kg/m² and not in the other BMI groups. Testing the interaction
between BMI and IGF-I level, we found significant results for

<table>
<thead>
<tr>
<th>Examined Variable</th>
<th>Grip strength</th>
<th>P</th>
<th>Grip strength</th>
<th>P</th>
<th>Grip strength</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI &lt;25 kg/m²</td>
<td>30.3 ± 1.2</td>
<td>0.88</td>
<td>32.8 ± 1.5</td>
<td>0.09</td>
<td>29.2 ± 2.0</td>
<td>0.03</td>
</tr>
<tr>
<td>BMI 25–29.9 kg/m²</td>
<td>30.0 ± 1.3</td>
<td>0.36</td>
<td>36.5 ± 1.4</td>
<td>0.06</td>
<td>35.2 ± 1.6</td>
<td>0.01</td>
</tr>
<tr>
<td>BMI ≥30 kg/m²</td>
<td>29.3 ± 1.2</td>
<td>0.31</td>
<td>34.4 ± 1.5</td>
<td>0.69</td>
<td>29.7 ± 2.1</td>
<td>0.08</td>
</tr>
</tbody>
</table>

Values are adjusted means ± SE in kg. IGFBP, insulin-like growth factor-binding protein. Means were adjusted for age, gender, cognitive performance scale score, physical activity, no. of diseases, osteoarthritis, ischemic heart disease, cancer, diabetes, serum LDL, and C-reactive protein (log transformed).
all study outcomes, suggesting that BMI could modify the association of IGF-I with hand grip strength, walking speed, and SPPB score. By contrast, independently of BMI, no association was observed between IGFBP-3 and study outcomes in the fully adjusted model, and no significant interaction was detected between BMI and IGFBP-3.

In the whole sample, only 20 participants had a BMI < 18.5 kg/m². In this group, the median value of free IGF-I was 0.48 ng/ml (IQR 0.27–0.79), the median value of IGFBP-3 was 3,293 ng/ml (IQR 2,996–4,184), and the median value of C-reactive protein was 4.5 pg/ml (IQR 1.6–6.9). Analyzing participants in this group separately, we found that, in opposition to what observed in the group with BMI ≥ 30 kg/m², subjects with low IGF-I (n = 15) had better performance in grip strength (26.5 ± 10.2 vs. 22.7 ± 22.2 kg, P = 0.93), walking speed (0.46 ± 0.09 vs. 0.08 ± 0.15 m/s, P = 0.16), and SPPB score (1.4 ± 0.1 vs. 0.6 ± 0.2 m/s, P = 0.02) compared with those with high IGF-I (n = 5). Testing the interaction between the four-level variable for BMI (including a level for BMI < 18.5 kg/m²) and IGF-I level, we still found significant results for all study outcomes. By contrast, no association was observed between IGFBP-3 and study outcomes in the group of participants with BMI < 18.5 kg/m², and no significant interaction was found between the four-level variable for BMI and IGFBP-3.

DISCUSSION

The present study shows that obesity modifies the association between IGF-I and physical function. More specifically, among obese older adults, high IGF-I is associated with better physical performance and muscle strength compared with low IGF-I, but this association was not consistent among nonobese subjects. No relationship was observed between IGFBP-3 and study outcomes, independently of BMI.

This is the first study to assess the association between IGF-I and physical function in the very old and to evaluate the effect of BMI on this association. Previous observations examining the association of IGF-I with muscle strength and physical performance in younger populations have provided conflicting results, but none of these studies has examined the role played by obesity on this relationship (3, 5, 16, 18). Indeed, among obese men and women, the administration of GH, which is the primary determinant of IGF-I production, resulted in a reduced amount of visceral fat and increased muscle area (9, 17). Interestingly, in a study among obese postmenopausal women, the administration of GH alone or in combination with IGF-I caused a greater increase in fat-free mass and a greater reduction in fat mass than those achieved by diet and exercise alone (35). In addition, both GH and IGF-I have been shown to improve serum lipid pattern and insulin sensitivity and to protect against endothelial dysfunction, atherosclerotic plaque development, and ischemic myocardial damage (7). These effects may probably result in greater benefits among obese older adults that are at higher risk for cardiovascular and metabolic diseases.

The fact that clinical applications of these findings are limited by safety issues is noteworthy. Recent studies have found that IGF-I correlates with risk of prostate cancer in men, premenopausal breast cancer in women, and lung cancer and colorectal cancer in both men and women (30). However, results of the present study may help to identify subjects who may obtain a greater benefit from receiving IGF-I, leading to a reduced risk-to-benefit ratio for this treatment.

By contrast, we found no correlation between serum IGFBP-3 concentration and measures of physical performance and muscle strength, irrespective BMI. This finding agrees with previous reports, suggesting that IGFBP-3 may have a limited role in the processes leading to loss of physical function, and it can only represent an indicator of increased catabolism and wasting (11). However, it cannot be excluded that the effect of IGFBP-3 on study outcomes is smaller than we can detect, and significant differences could be observed with a larger sample size.

Table 4. Association of Short Physical Performance Battery score with IGF-I and IGFBP-3 according to BMI

<table>
<thead>
<tr>
<th>Examined Variable</th>
<th>BMI &lt;25 kg/m²</th>
<th>BMI 25–29.9 kg/m²</th>
<th>BMI ≥30 kg/m²</th>
<th>P for Interaction Between BMI and Examined Variable</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>SPPB score</td>
<td>P</td>
<td>SPPB score</td>
<td>P</td>
</tr>
<tr>
<td>Low free IGF-1</td>
<td>1.6 ± 0.1</td>
<td>0.86</td>
<td>1.8 ± 0.1</td>
<td>0.86</td>
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<tr>
<td>High free IGF-1</td>
<td>1.6 ± 0.1</td>
<td>1.7 ± 0.1</td>
<td>1.7 ± 0.1</td>
<td>1.54</td>
</tr>
<tr>
<td>Low IGFBP-3</td>
<td>1.5 ± 0.1</td>
<td>0.51</td>
<td>1.7 ± 0.1</td>
<td>0.54</td>
</tr>
<tr>
<td>High IGFBP-3</td>
<td>1.6 ± 0.1</td>
<td></td>
<td>1.8 ± 0.1</td>
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</tbody>
</table>

Values are adjusted means ± SE. Means were adjusted for age, sex, cognitive performance scale score, physical activity, no. of diseases, osteoarthritis, ischemic heart disease, cancer, diabetes, serum LDL, and C-reactive protein (log transformed).

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To assess the effect of IGF-I and IGFBP-3 on physical function, we used the hand grip strength and physical performance tests. These measures of physical function provide a “multidimensional,” objective, and standardized assessment of older persons, they are able to characterize community-dwelling older people across a broad spectrum of functional status, and they are very sensible to changes over time (12, 25, 27). In addition, several studies indicated that physical performance measures can complement self-reported measures in the assessment of older persons’ functional status, as suggested by the fact that they tap different but important dimensions of physical function (34).

In this study, we used grip strength as an indicator of general strength. Although being a direct measure of hand strength, grip strength has frequently been used as an overall measure of body strength because it is a reliable and easy-to-administer measure of strength that can be tested in a home setting (1, 31).

Physical function measures have gained increased acceptance and use for the clinical evaluation of older persons. In addition, it has been consistently demonstrated that measures of physical function can predict major health-related outcomes in the elderly, such as disability, death, and institutionalization (13, 25, 26, 29). For these reasons, adding an evaluation of physical function to the traditional clinical examination is particularly important in the assessment of older persons. However, the use of these tests in the clinical setting has not been widely adopted, possibly because of the misconception that they often require substantial space, special equipment, or are unduly time consuming.

It may be argued that the present findings are based on determination of free IGF-I, rather than on total IGF-I. However, it is widely accepted that free rather than total circulating IGF-I is biologically active and that free IGF-I determines the feedback on GH release in normal subjects (6).

In the study sample, C-reactive protein is slightly but not significantly higher in participants with BMI between 25 and 29.9 and ≥30 kg/m² compared with those with BMI < 25 kg/m². Given the well-known association between adiposity and chronic inflammation, a much stronger association would be expected. However, it should be considered that participants with elevated BMI were significantly younger and more physically active than those with normal or low BMI. Indeed, young age and physical activity were shown to reduce levels of inflammation; therefore, these factors may have reduced and flattened differences in C-reactive protein levels among BMI groups (8, 32).

The present study has several limitations. First, the cross-sectional design of the study does not allow clarification of any cause-effect mechanism. Second, despite the fact that the analyses were adjusted for many health- and disease-related characteristics, there could be unmeasured confounders that were not considered in this study. Furthermore, we had no direct measure of adiposity or of lean body mass, and we had no measure of central adiposity, such as the waist-to-hip ratio. The BMI cannot distinguish adequately between fat mass and lean tissue mass, and it may be a less useful indicator of adiposity among the older patients who have a greater amount of body fat at a given BMI than younger ones because of the age-related decline in muscle mass. Finally, the SIRENTE sample population was composed by persons aged 80 yr or older, so our results may not be applicable to other age groups.

In conclusion, the present study shows that the association of IGF-I and physical performance differs according to BMI. Future studies are needed to better evaluate the role played by obesity on the relationship of IGF-I and physical function and to investigate interventions aimed at the prevention of obesity-related physical decline through the modification of the growth hormonal axis.

REFERENCES