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INSULIN-LIKE GROWTH FACTOR-1 AND ANEMIA IN OLDER SUBJECTS: THE InCHIANTI STUDY

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Abstract

Objective—Recent studies indicate a role for the age-related decline of anabolic hormones, especially testosterone, in the onset of “anemia of aging.” Some of testosterone’s erythropoietic activities are mediated by insulin-like growth factor (IGF)-1, which also seems to have independent erythropoietic effects. However, the associations among IGF-1, anemia, and hemoglobin (Hb) have not been adequately investigated in older populations.

Methods—We used data from a representative sample of 953 subjects 65 years who participated in the InCHIANTI (Invecchiare in Chianti) Study and were not on growth hormone (GH) or erythropoietin therapy and were not diagnosed with hematologic malignancies or other cancers. Anemia was defined according to the World Health Organization (WHO) criteria by Hb level 13 g/dL in males and 12 g/dL in females. Backward multiple regression analyses including age, IGF binding protein (IGFBP)-3, testosterone, comorbidities, inflammatory markers, and anemia-related measures were used to address the relationship between IGF-1 and Hb and between IGF-1 and anemia in both sexes.

Results—We found that 46/410 (11.2%) males and 71/543 (13.0%) females were defined as anemic. After adjustment for age, anemic males (100 ± 54 vs. 130 ± 56 , $P < .001$) and females (89.1 ± 48 vs. 110 ± 52 , $P = .001$) exhibited lower IGF-1 levels than their nonanemic counterparts. IGF-1 levels were independently and negatively associated with anemia in males ($\beta \pm SE = -0.0005 \pm 0.0002$, $P = .04$) but not in females ($\beta \pm SE = -0.0002 \pm 0.0002$, $P = .40$). In both males ($\beta \pm SE = 0.002 \pm 0.001$, $P = .03$) and females ($\beta \pm SE = 0.002 \pm 0.0009$, $P = .03$), IGF-1 levels were independently and positively associated with Hb levels.

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DISCLOSURE

The authors have no multiplicity of interest to disclose.

Conclusion—In older males but not in females, IGF-1 levels are negatively associated with anemia. IGF-1 levels are independent and positive determinants of Hb concentration in both sexes.

INTRODUCTION

Anemia is a multifactorial condition defined by the World Health Organization (WHO) as hemoglobin (Hb) concentrations <13g/dL and <12 g/dL in males and females, respectively (1). The prevalence of anemia increases in both sexes after the fifth decade of life and is a highly prevalent condition in older adults (2). Data from the Third National Health and Nutrition Examination Survey (NHANES III) estimates that anemia affects 11% of community-dwelling older males and 10.2% of females, reaching 40% among the oldest-old (> 85 years) (3). Anemia in the elderly has emerged as an important healthcare issue that predicts a variety of adverse outcomes including hospitalization, decreased physical performance and muscle strength (4), increased risk of recurrent falls (5), frailty status (6), and mortality (7).

Chronic inflammation, chronic kidney disease, and nutrient deficiencies are well-known and common determinants of anemia in all age groups (8). However, identifying a single reason explaining anemia in elderly subjects is often difficult. Efforts to understand the pathophysiology of the so called “anemia of aging” have largely focused on the potential contributions of inflammatory pathways, erythropoietin resistance, and low stem cell proliferation rate (9). However, recent studies have pointed out the contribution of the age-related decline in anabolic hormone levels, especially testosterone, to the onset of anemia in both older males and females (10–11). Interestingly, some of testosterone anabolic activities, including erythropoiesis, seem to be mediated by Insulin-like growth factor (IGF)-1 (11).

There is in vitro and in vivo evidence of IGF-1 receptors in both precursors and mature erythrocytes, suggesting an independent erythropoietic effect of IGF-1 (12). In fact, IGF-1 seems to be involved in regulating normal and malignant hematopoiesis, granulopoiesis, and lymphopoiesis through its specific binding with 2 high-affinity receptors (13–14). Specifically, IGF-1 directly stimulates the proliferation and differentiation of the late stage of primitive and/or early erythroid progenitor cells in vitro (15–17). In young and adult subjects, low IGF-1 levels are considered a plausible causal factor of anemia under physiologic and pathologic conditions. In healthy prepubertal or early pubertal boys, IGF-1 levels have been positively correlated with blood Hb concentrations (18). There are similar data in children with short stature (19), growth hormone (GH)-deficient adults (20) and those affected by chronic kidney diseases (21). Thus, it could be hypothesized that reduced GH/IGF axis activity during aging negatively affects erythropoiesis in the elderly. However, just 1 study conducted in young-old subjects (70 years old) reported a significant inverse association between IGF-1 and Hb concentrations (22). Moreover, the potential role of IGF-1 as independent determinant of anemia has never been investigated in older population. Given the lack of data assessing the associations between anemia and IGF-1 and Hb levels, we addressed this hypothesis in a well-characterized, large cohort of elderly Italian subjects.

METHODS

Patients

InCHIANTI (Invecchiare in Chianti) is an epidemiological study of risk factors for mobility-disability in the elderly; it was designed by the Laboratory of Clinical Epidemiology of the Italian Research Council of Aging (Florence) and conducted in a representative sample of subjects living in Greve in Chianti and Bagno a Ripoli, 2 small towns in the Chianti geographic area (Tuscany, Italy).

The original population was composed of 1,453 participants (aged 22–104) who were randomly selected from the residents of these 2 municipalities using a multistage stratified sampling method. Data collection started in September 1998 and was completed in March 2000. Detailed information on the study design and data collection has been described elsewhere (23). From the initial sample of 1,256 eligible individuals aged more than 65 years, 1,155 agreed to participate. A total of 1,055 (83% of those originally eligible) provided a blood sample and had complete data on body mass index (BMI); caloric intake; serum concentrations of IGF-1, IGF binding protein (IGFBP)-3, testosterone, soluble transferrin receptor (sTfr), erythropoietin, interleukin (IL)-6, cyanocobalamin (vitamin B12), ferritin, folic acid, and iron; and creatinine clearance.

For the present study, 102 participants were excluded because of a positive medical history for cancer, gastrointestinal disease, or medical condition potentially associated with bleeding.

Anemia was defined according to the WHO criteria as a hemoglobin level less than 130 g/L (13 g/dL) in males and less than 120 g/L (12 g/dL) in females (1).

The final study population included 953 subjects (410 males and 543 females). None of the remaining participants were on erythropoietin; GH; corticosteroids; or iron, vitamin B12, or folate supplements. Participants did not have hematological malignancies or thalassemia traits. Participants received an extensive description of the study and only participated after providing written informed consent. The study protocol complied with the Declaration of Helsinki and was approved by the Institutional Review Board of the Italian National Institute of Research and Care of Aging.

Hormone Measurement

Blood samples were obtained from participants after a 12-hour fast and after a 15-minute rest. Aliquots of serum were stored at -80°C and were not thawed until analyzed. Serum total IGF-1 levels were measured at enrollment with immunoradiometric assays using commercial reagents from Diagnostic Systems Laboratories (Webster, TX). The inter- and intra-assay coefficients of variation (CVs) for 3 different concentrations (low, medium, and high) were all $<10\%$. The minimum detectable concentration (MDC) was 0.80 ng/mL. Serum IGFBP-3 was measured with a DSL-6600 ACTIVE Coated-Tube Immunoradiometric Assay kit. The MDC of IGFBP-3 was approximately 0.5 ng/mL. The intra- and interassay CVs were less than 4% and 2%, respectively. Total testosterone was assayed using commercial radioimmunologic kits from Diagnostic Systems Laboratories. The MDC was

0.08 nmol/L, and the intra- and interassay CVs for 3 different concentrations were 9.6, 8.1, and 7.8% and 8.6, 9.1, and 8.4%, respectively.

Anemia-Related Measures

Hemoglobin levels were analyzed within 4 hours of blood drawing using a SYSMEX SE-9000 autoanalyzer (Sysmex Corporation, Kobe, Japan). Erythropoietin was measured in duplicate by Quest Laboratories (Baltimore, MD) using the Advantage erythropoietin chemiluminescence immunoassay (Nichols Institute Diagnostics, San Clemente, CA), which has a sensitivity of 1.2 mU/mL and a CV <6%. The mean of the 2 assays was used in the analysis. Folic acid and vitamin B12 levels were measured by a radioimmunologic assay (ICN Pharmaceuticals, New York, NY). The MDCs were 0.6 ng/mL for folic acid and 25 pg/mL for vitamin B12; the interassay CVs were 7.1% and 12.3%, respectively. Vitamin B12 deficiency was defined as a concentration <200 pg/mL, and subjects were considered to be folate deficient at a concentration <2.2 ng/mL. Serum ferritin and sTfr levels were measured in duplicate using chemiluminescent immunoassays (Abbott Diagnostics, Abbott Park, IL and Nichols Institute Diagnostics). The MDCs for these methods were 5 ng/mL for ferritin and 0.1 nmol/L for sTfr, with CVs <7% for both methods. Circulating iron levels were assessed by a colorimetric assay (Roche Diagnostics, GmbH, Mannheim, Germany), with a sensitivity of 5 µg/dL and a CV <3%.

Inflammatory Markers

Serum IL-6 was measured in duplicate by high-sensitivity enzyme-linked immunosorbent assays (ELISAs) using commercial kits (human sIL-6R kits from BioSource International, Camarillo, CA). The MDC was 0.1 pg/mL and the interassay CV was 4.5%. C-reactive protein (CRP) was measured in duplicate using an ELISA and colorimetric competitive immunoassay that used purified protein and polyclonal anti-CRP antibodies. The MDC was 0.03 mg/L, and the interassay CV was 5%.

Comorbid Conditions and Other Measures

A clinician ascertained hematological malignancy according to pre-established criteria that combined information from physician diagnoses, pharmacological treatment, medical records, clinical examinations, and blood test results. Serum creatinine and urinary creatinine from the 24-hour urine collection were measured using a modified Jaffe method. Creatinine clearance was calculated as a measure of glomerular filtration rate.

Fasting insulin was determined on plasma sample stored -80°C by using a commercial double-antibody, solid-phase radioimmunoassay (Sorin Biomedica, Milan, Italy). Weight was measured to the nearest 0.1 kg using a high-precision mechanical scale with the participant wearing light clothes and without shoes. Standing height without shoes was measured to the nearest 0.1 cm. BMI was calculated as weight (kg)/height (m)². Daily caloric (kCal/day) intake was estimated by the European Prospective Investigation into Cancer and Nutrition Food Frequency Questionnaire (24).

Causes of Anemia

Anemia and its pathophysiologic forms were classified by sequentially applying the following criteria (25): (1) females with Hb <120 g/L (12 g/dL) and males with Hb <130 g/L (13 g/dL) were considered as anemic, (2) anemic participants with creatinine clearance <30 mL/minute were classified as having anemia of chronic kidney disease, (3) those with Tfr/log(ferritin) ratio >1.5 and/or ferritin <12 ng/mL were classified as having iron deficiency anemia, (4) those with low circulating iron (10.74 μ M [60 μ g/dL]) and no evidence of iron deficiency (Tfr/log[ferritin] <1.5) were classified as having anemia of inflammation, and (5) anemic participants with serum folate <2.2 ng/mL or vitamin B12 <147.56 pM (200 pg/mL) were classified as having nutritional ("B12/folate deficiency") anemia. Participants with normal renal function; normal circulating iron; and no iron, folate, or vitamin B12 deficiency (namely, lack of criteria usually associated with anemia of kidney disease, anemia of inflammation, or nutrient deficiency anemia) were classified as having "unexplained anemia of aging" (26).

Statistical Analysis

Normally distributed variables are reported as means $\pm$ SDs. To approximate normal distributions, log-transformed values for erythropoietin and IL-6 were used in the analysis and back-transformed for data presentation.

Differences in IGF-1 levels and other parameters among female and male subjects with anemia and without anemia as defined according to WHO criteria were tested by an age-adjusted linear regression model.

Hb levels were also categorized into quartiles based on distributions in the female and male study populations. Differences in IGF-1 levels across Hb quartiles were determined by using analysis of variance and tests for trend after adjustment for age.

Backward multiple regression analyses including age, BMI, IGFBP-3, insulin, testosterone, iron, sTfr, ferritin, folic acid, vitamin B12, erythropoietin, IL-6, caloric intake, and creatinine clearance were used to address the associations between IGF-1 and Hb and between IGF-1 and anemia in the 2 sexes.

Differences were considered statistically significant at $P < .05$. SAS 8.2 statistical package was used for all analyses (SAS Institute, Inc, Cary, NC).

RESULTS

The baseline study characteristics of the study participants are presented in Table 1. The mean ($\pm$ SD) ages of all males and females were 74.7 ± 7.0 and 76.5 ± 7.7 , respectively. Both anemic males and females were older than their nonanemic counterparts. Of the 953 study participants, 46 out of 410 (11.2%) males and 71 out of 543 (13.0%) females were defined as anemic according to WHO criteria.

Nine (19.5%) males and 23 (32.4%) females were classified as having anemia of chronic kidney disease. Two (4.3%) males and 1 (1.4%) female were classified as having anemia of

inflammation. Ten (21.7%) males and 7 (9.9%) females were classified as having iron deficiency anemia. Twenty-five (54.3%) males and 32 (45.0%) females were classified as having nutritional anemia. Finally, 8 (11.3%) females and 0 males were affected by unexplained anemia. Independent of age, anemic males (100.1 ± 54.0 vs. 130.2 ± 56.1 , $P < .001$) and females (89.1 ± 48.0 vs. 110.3 ± 52.0 , $P = .001$) exhibited significantly lower IGF-1 levels compared to their nonanemic counterparts. Anemic subjects of both sexes also exhibited significantly lower BMI, caloric intake, iron levels, and creatinine clearance and higher IL-6, CRP, and erythropoietin concentrations.

In the analyses stratified by serum Hb quartiles, IGF-1 levels were progressively higher with increasing quartiles of Hb in both females (Fig. 1 A) and males (Fig. 1 B) (P for trend $< .0001$). In a backward multivariate linear regression analysis adjusted for multiple confounders including IGFBP-3, testosterone, sTfr, log(erythropoietin), log(IL-6), BMI, caloric intake, vitamin B12, folic acid, ferritin, insulin, iron, and creatinine clearance, IGF-1 was independently and negatively associated with anemia in males ($\beta \pm SE = -0.0005 \pm 0.0002$, $P = .04$) but not in females ($\beta \pm SE = -0.0002 \pm 0.0002$, $P = .40$) (Table 2). BMI and iron levels were negatively associated with anemia in both sexes. In females, log(erythropoietin) and log(IL-6) were positively and negatively associated with anemia, respectively. In males, sTfr was positively and independently associated with anemia.

IGFBP-3, CRP, caloric intake, testosterone, ferritin, vitamin B12, folic acid, and creatinine clearance were not significantly associated with anemia in either sex. Serum IGF-1 levels were independently and positively associated with serum Hb concentration in males ($\beta \pm SE = 0.002 \pm 0.001$, $P = .03$) and females ($\beta \pm SE = 0.002 \pm 0.0009$, $P = .003$) (Table 3). BMI and iron and testosterone levels were also independently and positively correlated with Hb levels, whereas, age, log(erythropoietin), and CRP turned out to have an independent and negative correlation with Hb in both sexes (Table 3). IGFBP-3 was independently and positively associated with Hb in males ($\beta \pm SE = 0.01 \pm 0.005$, $P = .04$) and negatively associated in females ($\beta \pm SE = -0.01 \pm 0.004$, $P = .03$).

DISCUSSION

In a large community-based study of older subjects, we found a negative and independent association between IGF-1 and anemia in males and a positive and independent association between IGF-1 and Hb concentration in both sexes. This is the first study performed in older subjects to address the relationship between IGF-1 and anemia. It can be also considered a further attempt to provide evidence on the positive association between IGF-1 and Hb concentrations.

Our findings are consistent with those of the only population-based study available in the literature (22). Nilsson-Ehle and colleagues (22) assessed a cohort of 297 community-dwelling young-old subjects (aged 70 years old) and showed that IGF-1 but not IGFBP-3 levels were significant determinants of Hb concentration independent of erythropoietin, sex, and health status. However, these authors did not take into account the role of important confounders including testosterone, caloric intake, and inflammation, which were all considered in the present study.

Previous investigations were conducted in adult and young subjects affected by several clinical conditions. These studies documented a role for reduced GH/IGF axis activity in the development of the mild anemia. Data from GH-deficient adult individuals (20) and subjects affected by chronic renal failure (27) have shown that IGF-1 is a potential determinant of erythropoiesis. Similarly, Succurro et al (28) detected a 2.49-fold higher risk of anemia in nondiabetic adult subjects with IGF-1 levels in the lowest quartile, suggesting that low IGF-1 might be an important contributor to mild anemia.

IGF-1 could exert erythropoietic activities by multiple potential mechanisms. The decline in IGF-1 can influence lower erythroid cell growth and differentiation from bone marrow or peripheral blood (15–17). Alternatively, the decline in IGF-1 might account for the reduced erythropoietin activity (29) and iron metabolism (30).

We found lower IGF-1 levels in anemic participants of both sexes independent of age. Interestingly, IGF-1 was only negatively associated with anemia in males. This finding would suggest a potential sex-related role of IGF-1 in the anemia of the elderly, with a more prominent effect in males. This data is supported by the sex-specific trajectories of IGF-1 levels observed across the lifespan. Females of childbearing age usually show higher serum IGF-1 than males (31). In both sexes, daily spontaneous GH secretion is reduced by 50 to 70% with a subsequent reduction in IGF-1 levels after the age of 65. However, males at this age have higher IGF-1 levels than females (31).

IGF-1 can be considered to be at the crossroads of many stimuli other than GH, including other anabolic hormones such as testosterone (32). It is interesting to note that the relationship between IGF-1 and anemia was independent of testosterone. Based on previous investigations, we can hypothesize that testosterone and IGF-1 independently contribute to erythropoiesis maintenance in older individuals. In previous InCHIANTI analyses, testosterone was an independent predictor of anemia in both sexes (10); however, these were not adjusted for IGF-1. Taken together, these findings underline the importance of considering the overall anabolic hormonal contribution to the anemia of ageing (32). In this regard, we previously reported that the parallel decline in multiple anabolic hormones including testosterone and IGF-1 was found a more powerful predictor of mortality than a single hormonal derangement in older subjects (33).

We also observed an independent and positive association between IGFBP-3 and Hb in males and a negative association in females. This data is only partially consistent with the existing data from studies of community-dwelling older subjects (23,34). Individuals from the Aging and Longevity in the Sirente Geographic Area (ilSIRENTE) with IGFBP-3 concentrations >145.95 nmol/L showed a significantly higher mean Hb concentration compared to those with lower IGFBP-3 levels (13.4 ± 1.4 nmol/L versus 12.9 ± 1.9 nmol/L, respectively; $P = .03$) (34). However, although IGFBP-3 is the storage protein for IGF-1 and is able to exert paracrine and autocrine actions on cellular growth via IGF-dependent and IGF-independent mechanisms (35), its role in erythropoiesis is unclear given the lack of additional studies in older individuals.

The cross-sectional nature of this study did not allow us to determine the direction of the association between IGF-1 and anemia. We cannot ignore the possibility that lower IGF-1 and anemia might result from a chronic, mild pro-inflammatory state characterized by elevated levels of pro-inflammatory markers such as IL-6 and CRP. This status is frequently observed in older subjects (36). To reinforce this point, we found that anemic subjects of both sexes had significantly higher IL-6 and CRP levels compared to their nonanemic counterparts, independent of age. Consistently, Ferrucci and colleagues reported a positive association between IL-6 and CRP and anemia and low iron status (25). Studies documented an inverse association between IGF-1 and IL-6 (37) suggesting that overexpressed IL-6 may downregulate IGF-1 and IGFBP-3 (38). Conversely, it has also been observed that adequate levels of IGF-1 are associated with reduced oxidative stress and inflammatory status (39).

Limitations and Strengths

Some limitations of the study must be acknowledged. Because of the cross-sectional design of the study, we cannot establish cause-effect relationships between IGF-1 and Hb levels and anemia. We should also consider that other definitions of anemia with different Hb cutoffs can be proposed and evaluated (40). However, to compare our findings with those previously reported (22,34), we used the WHO criteria to define anemia (1). Moreover, given the epidemiologic nature of this study, the etiologic classification of anemia was not based on clinical gold standards. Thus, diagnoses of iron deficiency, anemia secondary to vitamin B12 deficiency, and anemia of chronic inflammation/anemia of chronic disease should be confirmed by comprehensive clinical and laboratory assessments and clinical follow-up.

Despite these limitations, our study has multiple important strengths. To our knowledge, this is the first data regarding the relationship between IGF-1 and anemia in a large cohort of community-dwelling subjects of both sexes. The population evaluated here had detailed and complete data on serum concentrations of factors known to influence IGF-1 levels and anemia including testosterone, IL-6, IGFBP-3, erythropoietin, BMI, caloric intake, vitamin B12, ferritin, folic acid, iron, and liver function that cannot be easily found in population studies of older adults.

CONCLUSION

In conclusion, in older males and females, IGF-1 levels are independently and positively associated with Hb concentration. In males but not females, IGF-1 levels are negatively associated with anemia. The contribution of IGF-1 to the development of anemia in aging requires additional investigation in prospective and intervention studies.

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Abbreviations

BMI	body mass index
CRP	C-reactive protein
CV	coefficient of variation
GH	growth hormone
Hb	hemoglobin
IGF-1	insulin-like growth factor-1
IGFBP-3	insulin-like growth factor binding protein-3
IL-6	interleukin-6
InCHIANTI	Invecchiare in Chianti
MDC	minimum detectable concentration
sTfr	soluble transferrin receptor

WHO World Health Organization

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Fig. 1. Serum mean IGF-1 levels by Hb quartiles. The figure shows the age-adjusted P values for mean IGF-1 levels across Hb quartiles in females (A) and males (B). The difference in IGF-1 levels across Hb quartiles was statistically significant in both sexes (test for trend, $P < .001$). *Hb* = hemoglobin; *IGF-1* = insulin-like growth factor-1.

Table 1Study Population Characteristics Stratified by Sex and the Presence of Anemia^a

Characteristics	Males (n = 410)			Females (n = 543)		
	Anemic	Not anemic	<i>p</i> ^b	Anemic	Not anemic	<i>p</i> ^b
n	46	364		71	472	
Age (years)	80.1 ± 8.4	74.2 ± 6.5	<.001	83.0 ± 9.2	75.0 ± 7.2	<.001
BMI (kg/m²)	25.9 ± 3.3	27.1 ± 3.3	.01	25.5 ± 4.3	27.9 ± 4.5	.02
Total IGF-1 (ng/mL)	100.1 ± 54.0	130.2 ± 56.1	<.001	89.1 ± 48.0	110.3 ± 52.0	.001
IGFBP-3 (ng/mL)	34.4 ± 13.0	39.8 ± 11.0	.28	41.9 ± 10.0	44.5 ± 10.7	.83
Creatinine clearance, mL/min	67.8 ± 32	84.9 ± 24.9	.03	58.6 ± 25.3	70.5 ± 23.3	.32
Fasting insulin (mIU/L)	11.0 ± 7.7	10.8 ± 5.7	.12	9.2 ± 5.7	11.7 ± 6.2	.004
Caloric intake (kCal/diet)	1,893.7 ± 454.1	2,181.2 ± 566.4	.01	1,622.4 ± 470.4	1,716.4 ± 468.3	<.001
Hemoglobin (g/dL)	11.4 ± 1.4	14.7 ± 0.9	<.0001	10.9 ± 0.9	13.4 ± 0.8	<.0001
Erythropoietin (mU/mL)	26.2 ± 24.8	11.0 ± 5.9	<.0001	15.5 ± 12.32	10.5 ± 5.03	<.0001
Iron (µg/dL)	55.9 ± 30.4	87.8 ± 25.8	.04	65.9 ± 26.4	83.4 ± 23.2	.08
Ferritin (ng/mL)	105.1 ± 115.9	193.4 ± 200.2	.83	104.6 ± 103.9	120.0 ± 102.2	.43
sTfr (nmol/L)	24.5 ± 15.1	16.1 ± 4.5	<.001	19.0 ± 9.1	16.7 ± 4.9	.09
Folic acid (ng/mL)	3.0 ± 2.0	3.0 ± 1.9	.13	3.4 ± 2.9	3.4 ± 1.9	.01
Vitamin B12 (pmol/L)	340.4 ± 312.3	315.3 ± 235.8	.28	373.6 ± 332.9	354.5 ± 249.3	.28
C-reactive protein (µg/mL)	12.7 ± 24.2	4.9 ± 8.2	.002	8.0 ± 13.9	4.5 ± 5.1	.005
Interleukin-6 (pg/mL)	7.7 ± 17.3	2.1 ± 2.2	.001	2.6 ± 2.9	1.9 ± 2.1	<.001
Testosterone (ng/dL)	370.6 ± 177.2	433.9 ± 122.1	.01	62.7 ± 30.7	59.1 ± 34.0	.49

Table 2

Determinants of Anemia in the Multivariate Analysis

	Males		Females	
	$\beta \pm SE$	p^a	$\beta \pm SE$	p^a
IGF-1	-0.0005 ± 0.0002	.04	-0.0002 ± 0.0002	.40
Log (erythropoietin)	0.05 ± 0.03	.07	0.07 ± 0.03	.02
BMI	-0.01 ± 0.004	.007	-0.007 ± 0.003	.04
Iron	-0.001 ± 0.0005	.05	-0.001 ± 0.0006	.02
sTfr	0.01 ± 0.002	<.001	-0.0004 ± 0.003	.88
Age	0.004 ± 0.002	.12	0.01 ± 0.002	<.001
Log (IL-6)	-0.0001 ± 0.02	.93	-0.05 ± 0.01	.008

Abbreviations: BMI, body mass index; CRP, C-reactive protein; IGF-1, insulin-like growth factor-1; IL-6, interleukin-6; sTfr, soluble transferrin receptor.

^aAdditional variables included in the model: IGFBP-3, CRP, caloric intake, insulin, testosterone, ferritin, vitamin B12, folic acid, and creatinine clearance.

Table 3

Determinants of Hemoglobin in the Multivariate Analysis

	Males		Females	
	$\beta \pm SE$	p^a	$\beta \pm SE$	p^a
IGF-1	0.002 ± 0.001	.03	0.002 ± 0.0009	.003
Age	-0.02 ± 0.009	.008	-0.02 ± 0.007	.001
Testosterone	0.19 ± 0.04	<.0001	0.31 ± 0.16	.04
Log (erythropoietin)	-0.41 ± 0.12	.001	-0.5 ± 0.10	<.001
BMI	0.09 ± 0.017	<.001	0.03 ± 0.01	.002
Iron	0.008 ± 0.002	.0001	0.01 ± 0.002	<.001
sTfr	-0.04 ± 0.01	<.001	0.008 ± 0.001	.41
IGFBP-3	0.01 ± 0.005	.04	-0.01 ± 0.004	.03
Insulin	0.005 ± 0.002	.82	0.02 ± 0.007	.009
Folic acid	0.006 ± 0.007	.42	-0.05 ± 0.02	.02
CRP	-0.10 ± 0.05	.03	-0.10 ± 0.05	.02

Abbreviations: BMI, body mass index; CRP, C-reactive protein; IGF-1, insulin-like growth factor-1; IGFBP-3, insulin-like growth factor binding protein-3; IL-6, interleukin-6; sTfr, soluble transferrin receptor.

^aAdditional variables included in the model: ferritin, caloric intake, vitamin B12, log (IL-6), and creatinine clearance.