Serum Insulin-like Growth Factor I and Risk for Heart Failure in Elderly Individuals without a Previous Myocardial Infarction: The Framingham Heart Study

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Background: **Several experimental investigations have emphasized the favorable effects of insulin-like growth factor I (IGF-I) on left ventricular remodeling, partly through its antiapoptotic effects. Cross-sectional clinical studies have reported that low serum IGF-I levels in patients with heart failure correlate with cachexia and severity of ventricular dysfunction. It is unclear whether low serum IGF-I is a risk factor for heart failure.**

Objective: **To prospectively study the association between serum IGF-I level and the incidence of congestive heart failure.**

Design: **Community-based, prospective cohort study.**

Setting: **Framingham, Massachusetts.**

Participants: **717 elderly individuals (mean age, 78.4 years; 67% women) who did not have myocardial infarction and congestive heart failure at baseline.**

Measurement: **Incidence of a first episode of congestive heart failure on follow-up.**

Results: **During follow-up (mean, 5.2 years), 56 participants (35 women) developed congestive heart failure. In multivariable Cox regression models adjusting for established risk factors at baseline, there was a 27% decrease in risk for heart failure for every 1 standard deviation increment in log IGF-I. Individuals with serum IGF-I level at or above the median value (140 μg/L) had half the risk for heart failure (hazard ratio, 0.49 [95% CI, 0.26 to 0.92]) of those with serum IGF-I levels below the median. These comparisons were maintained in analyses adjusting for the occurrence of a myocardial infarction on follow-up.**

Conclusions: **In our prospective, community-based investigation, serum IGF-I level was inversely related to the risk for congestive heart failure in elderly people without a previous myocardial infarction. Additional investigations are warranted to confirm these findings.**

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Considerable experimental and clinical evidence supports a key role of insulin-like growth factor I (IGF-I) in the pathogenesis of left ventricular remodeling and heart failure (1). In basic science studies, IGF-I promotes myocardial hypertrophy, increases cardiac contractility, and attenuates myocyte necrosis and apoptosis in models of ischemic, hemodynamic, and toxic cardiac injury (2–7). In clinical reports, patients with congestive heart failure have lower levels of serum IGF-I that correlate with the degree of left ventricular systolic dysfunction, presence of cachexia and skeletal muscle weakness, and indices of neurohormonal and cytokine activation (8, 9). Furthermore, administering IGF-I has been reported to improve left ventricular contractility indices in small clinical case series (10) and experimental models of heart failure (4).

Epidemiologic investigations have shown an increasing incidence of congestive heart failure with age (11). Serum IGF-I levels have been reported to decrease with age in community-based investigations (12, 13). These parallel observations suggest that a decrease in serum IGF-I level with age may increase the incidence of heart failure in the elderly (14). However, no previous investigation has prospectively examined the relationship of serum IGF-I level to the incidence of heart failure. We hypothesized, on the basis of the body of scientific evidence noted, that a low serum IGF-I level may be associated with an increased risk for congestive heart failure. Accordingly, we examined the relationship of serum IGF-I levels to the risk for congestive heart failure in an elderly, community-based sample.

Methods

Study Sample

The Framingham Heart Study began in 1948 as a prospective longitudinal epidemiologic investigation of 5209 women and men who are examined every 2 years (15). The 1167 participants who were alive at the time of the 22nd biennial examination cycle (between 1992 and 1994) were eligible for the present investigation. We excluded 450 participants (39%) for the following reasons: prevalent congestive heart failure (84 participants) or myocardial infarction (106 participants) and insufficient blood specimen for IGF-I analyses (260 participants). Participants with a myocardial infarction were excluded because low serum IGF-I level is a risk factor for myocardial infarction (16), which in turn is a powerful risk factor for heart failure (11). After the exclusions, 717 participants (mean age, 78.4 years; 479 women) were eligible.

At the baseline examination, all participants underwent a medical history, routine physical examination (including anthropometry and blood pressure measurement), 12-lead electrocardiography, and laboratory assessment of cardiovascular disease risk factors. The institutional review board at Boston Medical Center approved the study, and all participants gave written informed consent.

Measurement of Serum IGF-I

At the baseline examination, 3 mL of serum from each participant was obtained in the early afternoon (with the participant in a supine position and a nonfasting state). Specimens were immediately transported by courier from Framingham, Massachusetts, to the U.S. Department of Agriculture Human Nutrition Research Center on Aging at Tufts University, Boston, Massachusetts, and stored at −80° C. Serum on dry ice was then shipped to Endocrine Sciences, Inc. (Calabasas Hills, California). Serum IGF-I was measured by radioimmunoassay after acid ethanol extraction (17) in 3 batches; the intrassay coefficient of variation was less than 4%. Insulin-like growth factor–binding proteins were not measured.

Outcome

All participants were under continuous surveillance for the development of cardiovascular disease events, including congestive heart failure. Three experienced investigators reviewed all suspected congestive heart failure events by examining hospital records, information from physicians, and pathology reports by using previously described methods (18). Congestive heart failure was diagnosed on the basis of the previously detailed Framingham Heart Study criteria (19); these criteria, which require the simultaneous presence of at least 2 major criteria or 1 major criterion in conjunction with 2 minor criteria to diagnose heart failure, have been validated previously (20). Major criteria included paroxysmal nocturnal dyspnea or orthopnea, jugular venous distension, pulmonary rales, radiographic cardiomegaly, acute pulmonary edema, third heart sound, central venous pressure greater than 16 cm H_2O, hepatojugular reflux, and weight loss of at least 4.5 kg in 5 days in response to treatment of heart failure. Minor criteria included bilateral ankle edema, nocturnal cough, dyspnea on ordinary exertion, hepatomegaly, pleural effusion, and heart rate of 120 beats/min or greater. Minor criteria were acceptable only if they were not attributed to another medical condition (such as chronic lung disease, cirrhosis, ascites, or nephrotic syndrome).

Statistical Methods

We used multivariable Cox proportional hazards regression models (21) to examine the association of serum IGF-I with the incidence of congestive heart failure. Since there was no effect modification by sex, all analyses were performed for pooled sexes, with sex as a covariate. The distribution of serum IGF-I was slightly skewed positively, and raw values were log-transformed to reduce excessive influence of high values at the upper end of the distribution. Other investigators have used a similar approach (12, 22). Serum IGF-I was treated both as a continuous variable (raw value and with natural logarithmic transformation) and as a categorical variable (values below versus at or above the median value of 140 μg/L). Age- and sex-adjusted probabilities of developing congestive heart failure on follow-up were estimated for individuals with serum IGF-I values below versus at or above the median value of 140 μg/L from Cox regression models incorporating age and sex as covariates.

In multivariable analyses, we adjusted for the following covariates (defined at the baseline examination): age, sex, ratio of serum total cholesterol to high-density lipoprotein (HDL) cholesterol, diabetes mellitus, systolic and diastolic blood pressure, antihypertensive treatment, smoking status, body mass index, clinical valve disease, prevalent atrial fibrillation, electrocardiographic left ventricular hypertrophy, and prevalent cardiovascular disease other than myocardial infarction (individuals with myocardial infarction were excluded, as noted). All 717 participants had complete information on these covariates. Criteria for these covariates have been described previously (18).

We examined the following statistical models in hierarchical fashion: multivariable models with all covariates defined at baseline, as detailed, ignoring the occurrence of myocardial infarction on follow-up (model A); models adjusting for covariates at baseline and the occurrence of a myocardial infarction on follow-up (model B) (the latter adjustment is important because low serum IGF-I levels can predispose to the development of congestive heart failure by promoting myocardial infarction [16]); and models in which participants who experienced a myocardial infarction on follow-up were censored at the time of myocardial infarction (model C).

Hazard ratios and their 95% CIs were estimated for each SD increase in the log IGF-I and raw IGF-I, and for levels at or above 140 μg/L versus below (separately for each statistical model).

Context

Biological research and retrospective clinical studies show that insulin-like growth factor I (IGF-I) promotes salutary left ventricular modeling.

Contribution

This community-based study followed 717 elderly people without known myocardial infarction or heart failure for 5 to 9 years. Participants with higher levels of IGF-I developed heart failure less often than did those with lower levels.

Implications

High IGF-I levels are associated with decreased risks for heart failure.

Cautions

High IGF-I levels are also associated with increased risks for cancer. Future research should confirm these associations and explore mechanisms to increase IGF-I levels in people at risk for heart failure without increasing the risk for cancer.

–The Editors

Table 1. **Characteristics of Study Participants***

Variable	Men (*n* = 238)	Women (*n* = 479)
Age, *y*	77.9 ± 4.3	78.6 ± 4.6
Body mass index, *kg/m²*	27.0 ± 3.9	26.8 ± 5.1
Systolic blood pressure, *mm Hg*	144 ± 21	143 ± 20
Diastolic blood pressure, *mm Hg*	74 ± 11	72 ± 10
Hypertension, %	68.5	73.5
Hypertension treatment, %	43.0	50.5
Total cholesterol level, *mmol/L (mg/dL)*	5.0 ± 0.8 (193 ± 30)	5.5 ± 0.9 (214 ± 36)
HDL cholesterol level, *mmol/L (mg/dL)*	1.11 ± 0.37 (43.0 ± 14.1)	1.4 ± 0.4 (54.0 ± 15.9)
Total cholesterol–HDL cholesterol ratio	4.9 ± 1.5	4.3 ± 1.4
Diabetes, %	16.8	9.0
Smoking, %	6.7	9.6
Clinical valve disease, %†	7.1	5.2
Left ventricular hypertrophy on ECG, %‡	3.5	3.1
Prevalent atrial fibrillation, %	10.5	5.2
Prevalent cardiovascular disease, %§	27.3	22.3
Myocardial infarction on follow-up, %	8.4	4.4
Serum IGF-I level, *μg/L*	154.7 ± 64.0	138.4 ± 54.2
Log-transformed IGF-I, *log μg/L*	4.9 ± 0.5	4.8 ± 0.4

* Values expressed with a plus/minus sign are the mean ± SD. ECG = electrocardiography; HDL = high-density lipoprotein; IGF-I = insulin-like growth factor I.
† Systolic murmur of grade 3 or more (of 6) or any diastolic murmur.
‡ Voltage criteria and repolarization abnormalities.
§ Includes cerebrovascular disease, peripheral vascular disease, and coronary disease other than a recognized myocardial infarction (angina, coronary insufficiency, or unrecognized myocardial infarction).

Additional Analyses

In the statistical models adjusting for covariates defined at the baseline examination and occurrence of an interim myocardial infarction (model B), we performed analyses incorporating several interaction terms (serum IGF-I level × covariate) to examine for any variation in the effect of serum IGF-I on congestive heart failure hazard (effect modification) according to age, sex, body mass index, presence or absence of diabetes, and total cholesterol–HDL cholesterol ratio.

High IGF-I levels in conditions such as acromegaly may be associated with cardiac systolic and diastolic dysfunction (23). We therefore evaluated for any nonlinearity (U shape) in the relationship of serum IGF-I level to risk for congestive heart failure. Furthermore, since serum interleukin-6 has been reported to lower IGF-I levels (24) and cytokines have been implicated in the pathogenesis of congestive heart failure (25), we performed supplementary analyses adjusting for serum interleukin-6 in a subgroup of 525 individuals who had both serum interleukin-6 (enzyme-linked immunosorbent assay, R&D Systems, Minneapolis, Minnesota) and IGF-I measurements available. We performed secondary analyses in which death was modeled as a competing outcome to congestive heart failure (26), given the high mortality rate in our elderly cohort.

Although left ventricular systolic function was not assessed at the baseline examination, routine echocardiography was done at examination cycle 20, approximately 4 years from the baseline examination. Additional analyses were performed on a subgroup of individuals who attended examination cycle 20 and had normal left ventricular systolic function at that examination.

A 2-sided *P* value of 0.05 was considered significant. All analyses were performed by using SAS software, version 8.02 (SAS Institute, Inc., Cary, North Carolina).

Role of Funding Sources

The funding sources supported the collection of IGF-I data but played no role in the analysis or interpretation of the data or in the decision to submit the manuscript for publication.

RESULTS

Clinical Characteristics

Table 1 displays the baseline characteristics of our sample. In our elderly sample, about 70% of participants were hypertensive. Men had slightly higher serum IGF-I levels than women, as reported by other studies (12).

Serum IGF-I Level and Congestive Heart Failure Rate

During a mean follow-up of 5.2 years (maximum, 8.9 years), 56 individuals developed congestive heart failure. The **Figure** displays the age- and sex-adjusted probability of the development of congestive heart failure in study individuals, according to serum IGF levels below versus 140 μg/L or greater. The hazard of heart failure was noticeably higher for individuals with serum IGF-I levels below 140 μg/L.

After adjustment for known heart failure risk factors, there was a 27% lower hazard of congestive heart failure for every SD increment in log IGF-I (**Table 2**, *model A1*). Participants with serum IGF-I levels at or above 140 μg/L had a 51% lower hazard of congestive heart failure than that of those with serum IGF-I levels lower than 140 μg/L (**Table 2**, *model A2*). The association of serum IGF-I with risk for heart failure was maintained even after additional adjustment for an interim myocardial infarction (**Table 2**, *models B1 and B2*). In these models, a serum IGF-I level below 75 μg/L (corresponding to the 10th percentile value in our elderly sample) was associated with a more than 2.5-fold increased hazard of congestive heart failure (hazard ratio, 2.60 [95% CI, 1.19 to 5.68]; $P = 0.016$; covariates as in model B). Statistical models in which we censored individuals who had a myocardial infarction in the interim yielded similar results (**Table 2**, *models C1 and C2*). Analyses using untransformed IGF-I values yielded similar results. Hazard ratios for congestive heart failure per SD increment (58 μg/L) in raw IGF-I were 0.70 (CI, 0.51 to 0.96; $P = 0.03$) for model A, 0.66 (CI, 0.47 to 0.92; $P = 0.02$) for model B, and 0.67 (CI, 0.47 to 0.96; $P = 0.03$) for model C.

Additional Analyses

The effect of serum IGF-I level on congestive heart failure hazard did not vary with age, sex, body mass index, lipid status, or diabetes ($P > 0.05$ for all interactions). Furthermore, there was no evidence of nonlinearity in the relationship of serum IGF-I and congestive heart failure hazard. In supplementary multivariable analyses adjusting for serum interleukin-6 levels, the association of higher serum IGF-I level with a lower congestive heart failure hazard was maintained (**Table 3**).

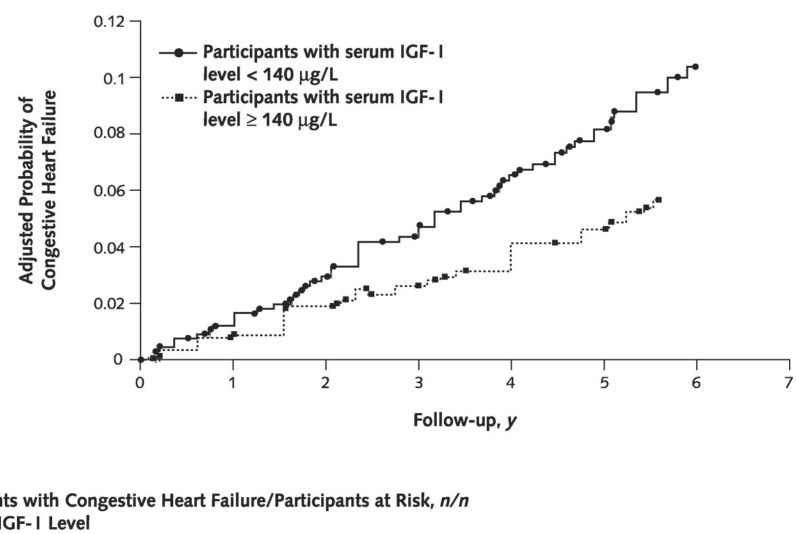
On follow-up, 289 individuals died; 76 people (10.6% of study sample; 26% of all deaths) died of cardiovascular causes. In additional analyses with death modeled as a competing outcome to congestive heart failure, the association between serum IGF-I level and congestive heart failure hazard remained robust.

Echocardiographic information on left ventricular systolic function was available at an examination 4 years before the baseline examination in 622 of 717 participants (87%). Only 3 of 622 participants had evidence of moderate or greater left ventricular systolic dysfunction at that examination. Information on all covariates for multivariable analyses was available on 580 of 619 participants without major left ventricular systolic dysfunction. Forty of these 580 participants developed congestive heart failure on follow-up. In multivariable models, each SD increment in log IGF-I was associated with a 23% to 26% lower hazard of congestive heart failure, consistent with the results of the primary analyses (hazard ratio, 0.74 [CI, 0.57 to 0.96], $P = 0.02$, for model A; 0.77 [CI, 0.58 to 1.01], $P = 0.06$, for model B; 0.74 [CI, 0.55 to 1.00], $P = 0.05$, for model C).

DISCUSSION

Several basic science reports have emphasized a fundamental role of IGF-I in regulating myocardial structure and function through its beneficial effects on cardiac myocyte survival, growth, calcium signaling, and differentiation (1, 2, 27). Overexpression of IGF-I has a salutary effect in

Figure. **Age- and sex-adjusted probability of developing congestive heart failure in participants according to serum insulin-like growth factor I (*IGF-I*) level at or above the median (140 μg/L).**



Participants with Congestive Heart Failure/Participants at Risk, *n/n*

Serum IGF-I Level < 140 μg/L	0/361	6/323	14/290	18/277	25/256	31/228	37/143
Serum IGF-I Level ≥ 140 μg/L	0/356	3/336	4/303	9/290	13/272	14/261	19/158

Adjusted probabilities are estimated by Cox proportional hazards regression with age and sex as covariates. The curves represent probabilities for typical participants (by sex and age) in the 2 serum IGF-I groups: participants with congestive heart failure and participants at risk with serum IGF-I level at or above the median (*dotted line*), 19 and 356 participants (5.3%), respectively, and participants with congestive heart failure and participants at risk with serum IGF-I level below the median (*solid line*), 37 and 361 participants (10.2%), respectively. The numbers of participants with congestive heart failure and participants still at risk at each year of follow-up are presented below the figure. Data are shown only through 6 years of follow-up.

Table 2. **Serum Insulin-like Growth Factor I Level and Risk for Congestive Heart Failure: Results of Multivariable Cox Models***

Model	Hazard Ratio (95% CI)	*P* Value
Model A†		
1. Per SD increment log IGF-I‡	0.73 (0.58–0.93)	0.01
2. IGF-I level ≥ 140 μg/L vs. below§	0.49 (0.26–0.92)	0.03
Model B‖		
1. Per SD increment log IGF-I‡	0.74 (0.58–0.95)	0.02
2. IGF-I level ≥ 140 μg/L vs. below§	0.52 (0.27–0.99)	0.05
Models C¶		
1. Per SD increment log IGF-I‡	0.73 (0.56–0.95)	0.02
2. IGF-I level ≥ 140 μg/L vs. below§	0.46 (0.23–0.91)	0.03

* All 3 models adjust for age, sex, diabetes, systolic blood pressure, hypertension treatment, smoking status, body mass index, total cholesterol–high-density lipoprotein cholesterol ratio, valve disease, prevalent atrial fibrillation, left ventricular hypertrophy on electrocardiography, and prevalent cardiovascular disease. IGF-I = insulin-like growth factor I.
† Model A: Multivariable models adjusting for covariates at baseline.
‡ One SD increment of log-transformed IGF-I (0.47 log-transformed IGF-I units [log μg/L]).
§ Hazard ratios associated with IGF-I level below 140 μg/L (vs. above) can be derived by taking the reciprocals: 2.04 (1.09–3.81), for model A; 1.94 (1.01–3.76), for model B; and 2.19 (1.10–4.37), for model C.
‖ Model B: Models adjusting for covariates at baseline and interim myocardial infarction (time-dependent).
¶ Model C: Models adjusting for covariates at baseline and censoring participants at time of interim myocardial infarction.

experimental models of heart failure (28–31). In clinical studies of patients with heart failure, IGF-I levels are low and correlate with the severity of ventricular systolic dysfunction and the degree of cachexia (8, 9). These experimental and clinical data suggest that IGF-I may be cardioprotective even in individuals without heart failure or clinically apparent myocardial injury. However, the contribution of serum IGF-I levels to risk for heart failure in the general population is unknown. The present investigation examined, for the first time, the association between serum IGF-I levels and risk for congestive heart failure in elderly individuals who did not have a previous myocardial infarction.

Principal Findings

A high serum IGF-I level was associated with a diminished hazard of heart failure in a continuous fashion without evidence of a threshold. A serum IGF-I level below 140 μg/L was associated with a doubling of the hazard of congestive heart failure, while a serum IGF-I level below 75 μg/L (corresponding to the 10th percentile in our sample) was associated with a 2.5-fold increased hazard. The decreased hazard of heart failure associated with increased IGF-I levels remained robust in analyses incorporating interim myocardial infarction as a time-dependent variable and in models censoring individuals at the time of an interim myocardial infarction. The relationship to congestive heart failure hazard persisted in analyses accounting for death as a competing event to congestive heart failure and in models adjusting for serum interleukin-6.

Mechanisms

The inverse relationship of serum IGF-I levels and hazard of congestive heart failure may be explained by indirect and direct effects of the peptide that positively influence cardiac structure and function. Indirect effects of IGF-I include its vasodilatory action that chronically maintains low arterial impedance (32).

Insulin-like growth factor I may directly and favorably affect left ventricular remodeling and function. Insulin-like

Table 3. **Conjoint Effects of Serum Insulin-like Growth Factor I and Interleukin-6 on Risk for Congestive Heart Failure: Results of Multivariable Cox Models***

Model	Hazard Ratio (95% CI)	*P* Value
Model A†		
1. Per SD increment log IGF-I‡	0.71 (0.53–0.93)	0.01
2. Per SD increment log interleukin-6‡	1.36 (1.09–1.70)	0.007
Model B§		
1. Per SD increment log IGF-I‡	0.70 (0.52–0.94)	0.02
2. Per SD increment log interleukin-6‡	1.34 (1.04–1.72)	0.02
Model C‖		
1. Per SD increment log IGF-I‡	0.75 (0.54–1.04)	0.08
2. Per SD increment log interleukin-6‡	1.41 (1.11–1.78)	0.004

* All 3 models adjust for age, sex, diabetes, systolic blood pressure, hypertension treatment, smoking status, body mass index, total cholesterol–high-density lipoprotein cholesterol ratio, valve disease, prevalent atrial fibrillation, left ventricular hypertrophy on electrocardiography, and prevalent cardiovascular disease. Data are on 37 congestive heart failure cases among 525 participants with both serum IGF-I and interleukin-6 values available. IGF-I = insulin-like growth factor I.
† Model A: Multivariable models adjusting for covariates at baseline.
‡ One SD increment of log-transformed IGF-I (0.48 log-transformed IGF-I units [log μg/L]). One SD increment of log-transformed interleukin-6 (0.64 log-transformed interleukin-6 units [log μg/L]).
§ Model B: Models adjusting for covariates at baseline and interim myocardial infarction (time-dependent).
‖ Model C: Models adjusting for covariates at baseline and censoring participants at time of interim myocardial infarction.

growth factor I receptors are expressed in the myocardium, where the peptide has autocrine and paracrine functions (1). Myocardial injury due to diverse insults (ischemia-reperfusion [5], hemodynamic pressure overload [6], or cardiotoxic agents [7]) is prevented by IGF-I infusion. In addition, increased expression of IGF-I is thought to positively influence myocyte survival by inhibiting apoptotic and activating survival pathways (33). Insulin-like growth factor I also promotes myofibrillar hypertrophy (3), thereby favorably influencing the capability of the heart to withstand hemodynamic stress. Beneficial effects of IGF-I overexpression have been reported consistently in acquired, as well as transgenic, models of heart failure (28, 31). Independent of remodeling, IGF-I has a positive inotropic effect that can improve myocardial contractile function (28, 31). While all these mechanisms may be operative, it is not entirely clear whether any particular cardioprotective action of IGF-I predominates.

Strengths and Limitations

The strengths of our investigation include the large community-based sample, the continuous surveillance of all participants for heart failure, and the use of the same criteria consistently for the diagnosis of heart failure. Nonetheless, our study has several limitations. We measured serum total IGF-I rather than the biologically active free IGF-I. We did not measure IGF-binding proteins. It is well known that the levels of IGF-binding proteins (especially IGF-binding protein-3) influence the effects of serum IGF-I on cardiovascular risk (16). However, serum IGF-I is highly correlated with the ratio of IGF-I to IGF-binding protein-3 (34), and the use of serum IGF-I alone may have resulted in an underestimation of the effect of serum IGF-I on risk for heart failure. We excluded institutionalized individuals who could not attend the index examination. Such individuals were sicker and more likely to have lower IGF-I levels; their exclusion would also result in a conservative bias. Finally, our study sample was almost exclusively white and elderly, reducing the generalizability of our findings to other ethnic groups and age groups.

Implications

Decrease in IGF-I level with age may contribute to the increase in cardiac disease in the elderly, including heart failure (14). Our investigation also supports this notion. The initial disappointing results of growth hormone infusions in patients with dilated cardiomyopathy (35) may have been related to the choice of the incorrect agent (growth hormone instead of IGF-I) or the failure to target patients with low IGF-I levels selectively (27).

If confirmed, our observational data suggest that maintenance of optimal levels of IGF-I in the elderly may reduce the risk for heart failure. In this context, it is important to note that high IGF-I levels have been associated with increased hazard of developing several common cancers, again because of its antiapoptotic effects (36, 37). Thus, although high serum IGF-I levels may prevent heart failure, such an approach may increase the hazard of cancer. Additional research is warranted to identify optimal IGF-I levels that are cardioprotective but do not elevate cancer hazard. A potential approach to increase IGF-I levels that may merit further exploration is through exercise (38).

Our findings suggest that a low serum IGF-I level is an important risk factor for congestive heart failure in elderly individuals without a previous myocardial infarction. Additional investigations are warranted to confirm these findings.

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