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High insulin-like growth factor binding protein-1 (IGFBP-1) level predicts incident congestive heart failure in the elderly

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Abstract

Background—Low insulin-like growth factor–1 (IGF-I) may influence the development of age-related cardiovascular diseases including congestive heart failure (CHF). Insulin-like growth factor binding protein-1 (IGFBP-1), which increases during catabolic states and inhibits anabolic IGF-I effects, is increased in CHF patients and has been associated prospectively with increased mortality among older adults and myocardial infarction survivors. We investigated the association between fasting plasma levels of IGF-I, IGFBP-1, IGFBP-3, and insulin and risk of incident CHF in the prospective Cardiovascular Health Study (CHS).

Methods—From among 5,888 65+ year-old adults in the Cardiovascular Health Study (CHS), we studied 566 incident CHF cases and 1,072 comparison subjects, after exclusion of underweight individuals (BMI < 18.5 kg/m^2) and insulin users. Hazard ratios (HR) with 95% confidence intervals (CIs) for CHF were estimated after adjustment for age, race, gender, hypertension, systolic blood pressure, lipid levels, left ventricular hypertrophy, coronary disease, C-reactive protein, health status, diabetes, and BMI.

Results—High baseline IGFBP-1 level was a significant predictor of CHF, independent of established CHF risk factors and inflammation markers. The HR per SD of IGFBP-1 was 1.22 (95% CI=1.07–1.39, p < 0.01). Relative to the lowest IGFBP-1 tertile, the HR was 1.29 (95% CI=0.96–1.74, p=0.09) for the second IGFBP-1 tertile and 1.47 (95% CI=1.06–2.04; p=0.02) for

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the highest IGFBP-1 tertile (tertile cutpoints 19.5 and 35.8 ng/ml). Total IGF-I, IGFBP-3, or insulin levels had no association with CHF after adjustment for CHF risk factors.

Conclusions—High circulating IGFBP-1 may be a CHF risk factor among older adults.

The insulin-like growth factor (IGF) system is highly conserved across species and plays a central role in cellular differentiation, cellular proliferation, apoptosis, metabolism, wound repair, and somatic growth (1–6). IGF-I, the main effector peptide of the IGF system and the principal mediator of growth hormone (GH) effects, may influence the development of age-related cardiovascular diseases (7–11). A report from the Framingham Heart Study identified low IGF-I as a risk factor for incident congestive heart failure (CHF) in the elderly (7). IGF binding proteins (IGFBPs) modulate IGF-I activity and may also have IGF-I-independent effects. Circulating IGFBP-3, like IGF-I, is responsive to GH status (12) and in older adults IGFBP-3 and IGF-I decline in concert with decreased GH. Most IGF-I in circulation is bound to IGFBP-3, suggesting a role of IGFBP-3 in determining the circulating half-life of IGF-I and its delivery to target tissues. IGFBP-1 is less abundant than IGFBP-3, but appears particularly important in regulating IGF-I bioavailability, with strong inverse correlations between circulating IGFBP-1 and free IGF-I (13) (14). IGFBP-1 has a very different system of regulation than IGFBP-3, with hepatic IGFBP-1 production strongly (inversely) regulated by insulin. Aging, cachectic conditions, malnutrition, inflammatory cytokines, and oxidative stress all increase IGFBP-1 expression (15–21), which may in turn lead to inhibition of anabolic IGF-I effects by IGFBP-1 during catabolic states. High circulating IGFBP-1 levels predict cardiovascular events after myocardial infarction (22) and cardiovascular mortality among apparently healthy older men (23). Prior data also indicate increased IGFBP-1 levels in CHF patients (24) which suggests that high circulating IGFBP-1 levels may be a CHF risk factor, although no prior studies of IGFBP-1 and incident CHF are available.

We assessed the association between fasting IGF-I, IGFBP-1, IGFBP-3, and insulin levels and incident CHF among older adults in the Cardiovascular Health Study (CHS).

METHODS

Study population and setting

CHS is a prospective population-based cohort study among 5,888 Medicare-eligible adults 65 years and older in four US communities (25). The original cohort of 5,201 participants was recruited in 1989–1990. In 1992–1993, 687 additional participants (mainly African-American) were recruited.

CHS participants completed standardized clinic examinations and questionnaires at study baseline and 9 annual visits. Data include medical history, use of prescription medications, and health-related behaviors. Physical exams included height, weight, blood pressures (BPs), and resting electrocardiograms (ECGs). Fasting blood specimens were obtained for storage at a central repository.

CHF events

All incident CHF events, as well as other vascular events, hospitalizations, and deaths, were identified through semi-annual participant contacts, notification by participants and proxies, and national databases (26). Medical records were centrally reviewed and classified. CHF was defined as a constellation of symptoms including shortness of breath, fatigue, orthopnea and paroxysmal nocturnal dyspnea and physical signs including edema, rales, tachycardia, a gallop rhythm and a displaced LV apical impulse. Criteria used to validate CHF diagnoses were: cardiomegaly and pulmonary edema on chest X-ray, evidence of a dilated ventricle,

and global or segmental wall-motion abnormalities with decreased systolic function either by echocardiography or contrast ventriculography (27, 28). Criteria required that the participant was treated medically for CHF. Medical records review collected information on left ventricular (LV) ejection fraction, presence of valvular heart disease, and other clinical characteristics.

Study subjects

We used a case-cohort study design to examine the relationship between baseline plasma levels of IGF-I, IGFBP-1, IGFBP-3, and insulin and risk of incident CHF. Using follow-up data through the end of CHS visits (June 30, 2001), we identified 607 participants with incident CHF. A random sample of 1,122 participants selected from the baseline study population served as the comparison group. Individuals who had had a history of myocardial infarction, stroke, or CHF at baseline were excluded from both the CHF case group and the random subcohort. Subjects with BMI < 18.5 kg/m^2 were excluded because low body mass is a marker of prevalent CHF, and nutritional deficiency and wasting affect IGF and insulin levels. We also excluded insulin users because of the difficulty of interpreting insulin and IGF levels in this group. After exclusions, 566 incident CHF cases and 1,072 subcohort members were included in the case-cohort analyses.

Laboratory methods

In 2005, fasting plasma specimens were analyzed for total IGF-I, IGFBP-1, and IGFBP-3 using enzyme-linked immunosorbent assay methods (ELISA) (DSL, Webster, TX) (29). Within-batch and between-batch coefficients of variation were 6.9% and 6.0% for IGF-I, 3.5% and 3.1% for IGFBP-1, and 6.0% and 3.6% for IGFBP-3. Other laboratory variables of interest, including fasting insulin, glucose, lipids, and inflammatory markers were measured at the core CHS laboratory (30). To assess within-individual stability of IGF levels over time, in a subset of participants we conducted repeated measures over 2–3 years and found Pearson correlation of r = 0.74 for IGFBP-1, r = 0.83 for IGF-I, and r = 0.83 for IGFBP-3.

Variable definitions

Diabetes was defined as use of diabetes medication, or fasting glucose level above 126 mg/dl. Fasting glucose levels of 110–126 mg/dl were defined as impaired fasting glucose (IFG). BMI was categorized as normal weight (18.5–25.0 kg/m^2), overweight (25.0–30.0 kg/m^2), and obese (>=30.0 kg/m^2). Treated hypertension was defined as reported diagnosis of hypertension with use of antihypertensive medications.

Statistical methods

In preliminary analyses, we examined distributions of IGF-I, IGFBPs, and insulin levels to identify outlying values and assess the need for normalizing transformations (IGFBP-1 departed slightly from normality and was not transformed; insulin was log-transformed). We estimated hazard ratios (HRs) and 95% confidence intervals (CIs) relating IGF-I, IGFBP-1, IGFBP-3, and insulin levels with incident CHF using Cox proportional hazards regression. We estimated HRs per standard deviation (SD) of IGFs and insulin, with p-values derived from models based on linear parameterizations, and also estimated HRs across tertiles, with category cutpoints defined according to the distributions in the overall CHS subcohort (IGF-I: 122.1 and 171.9 ng/ml, IGFBP-1: 19.5 and 35.8 ng/ml, IGFBP-3: 3655.1 and 4425.6 ng/ml, insulin: 10 and 15 IU/ml). Models were adjusted for age, race, gender, hypertension, systolic BP, high-density lipoproteincholesterol (HDL-c), low-density lipoprotein-cholesterol (LDL-c), total cholesterol, left ventricular hypertrophy based on ECG (ECG-LVH), coronary artery disease (CAD) (including angina or coronary revascularization), C-reactive protein (CRP), perceived health status, diabetes/IFG and BMI. Results were

affected little by additional adjustment for use of estrogens, diuretics, angiotensin-converting enzyme inhibitors, oral corticosteroids, aspirin, or thyroid hormones, liver disease, renal disease, serum creatinine, albumin, marital status, education, income, diastolic BP, alcohol use, smoking, atrial fibrillation, physical activity, triglycerides, fibrinogen, white blood cell count, activities of daily living (ADL) and instrumental activities of daily living (IADL) limitations. In further analyses, we found that IGF-I:IGFBP-1 and IGF:IGFBP-3 molar ratios did not contribute to prediction of incident CHF, and that simultaneous adjustment for IGF-I, IGFBP-1, IGFBP-3, and insulin levels also had no effect on the observed associations.

To account for heterogeneity in the etiology of CHF, we conducted separate analyses for CHF with preserved LV function (ejection fraction >45%) and CHF with reduced LV function (ejection fraction <=45%). Individuals with CHF due to valvular heart disease were categorized separately, although there were too few to permit separate analysis (n=14). To assess the impact of preexisting poor health on results, we repeated analyses after excluding subjects with self-reported poor or fair general health, or difficulties with ADL or IADLs.

To account for the use of case-cohort sampling methods to select individuals for IGF measurements, variance correction was applied (31). We found no departure from the model assumption of proportional hazards. Missing values were present in <=2% for all variables except income (missing=6%), and we used complete-case approaches to handle missing values. Statistical significance was defined as $p<0.05$.

RESULTS

Subject characteristics

Mean follow-up time among 566 incident CHF cases was 6.2 years (median 6.3 y, range 0.1–12.0 y), and mean follow-up time in the comparison subcohort (n=1072) was 9.3 years (median 11.1 y, range 0.1–12.1 y). Mean age at baseline was 74.3 years for CHF cases and 72.4 years for the subcohort (Table 1). High IGFBP-1 levels were associated with female gender, White non-Hispanic race/ethnicity, absence of diabetes/IFG, estrogen use, older age, lower BMI, higher HDL cholesterol, lower LDL cholesterol, and lower levels of insulin, IGF-I, and IGFBP-3 (Table 2).

Incident CHF

In age-, gender-, and race-adjusted analyses, the HR for incident CHF was 1.10 (95% CI=0.99–1.23, p=0.08) per SD of IGFBP-1. The HR was 1.14 (95% CI=1.02, 1.29, p=0.03) per SD of IGFBP-1 after additional adjustment for hypertension, systolic BP, HDL-c, LDL-c, total cholesterol, ECG-LVH, CAD, CRP, general health, and diabetes/IFG. After BMI was also added to the model, the HR per SD of IGFBP-1 was 1.22 (95% CI=1.07–1.39, $p < 0.01$). In final models, compared with subjects in the lowest IGFBP-1 tertile (T_1), the multivariate-adjusted HR was 1.29 (95% CI=0.96–1.74, p=0.09) for those in the second IGFBP-1 tertile (T_2) and 1.47 (95% CI=1.06–2.04; p=0.02) for those in the highest IGFBP-1 tertile (T_3).

Further analyses were conducted to assess the impact of preexisting poor health on the association between IGFBP-1 and CHF. Findings were somewhat weaker after exclusion of subjects in poor/fair health (HR per SD=1.14, 95% CI=0.97–1.33, p=0.11), with difficulties in ADLs (HR per SD=1.21, 95% CI=1.05–1.38, p=<0.01), and with difficulties in IADLs (HR per SD=1.17, 95% CI=1.01–1.36, p=0.04).

CHF was not significantly associated with levels of IGF-I (age-, sex- and race-adjusted model, HR per SD=1.05, 95% CI=0.94–1.17, p=0.42; fully adjusted model, HR=1.12, 95%

CI=0.99–1.26, p=0.07) or IGFBP-3 (age-, sex-, and race-adjusted model, HR per SD=1.00, 95% CI=0.89–1.13, p=0.95; fully adjusted model, HR=1.11, 95% CI=0.97–1.26, p=0.13). Insulin level was a significant predictor of CHF after adjustment for age, sex, and race (HR per SD ln[Insulin]=1.22, 95% CI=1.09–1.35, p<0.01), but not in the fully adjusted model (HR=0.95, 95% CI=0.81–1.10, p=0.47).

CHF subtypes

Among cases, 139 had CHF with preserved LV function, 141 had CHF with reduced LV function, 272 had CHF with unknown ejection fraction, and 14 had valvular heart disease. High IGFBP-1 was a significant predictor of CHF with preserved LV function (HR comparing T_3 versus T_1=1.90, 95% CI=1.11–3.28, p=0.02). Results for CHF with reduced LV function also suggested increased risk with high IGFBP-1 levels but did not achieve significance (HR comparing T_3 versus T_1=1.53, 95% CI=0.90–2.62, p=0.12). Confidence intervals for the two hazard ratios were overlapping.

DISCUSSION

Among older adults, high fasting IGFBP-1 level predicted increased risk of incident CHF. This association was independent of vascular risk factors, inflammation markers, and preexisting poor health status. Compared with the lowest IGFBP-1 tertile, the adjusted HR was 1.29 (p=0.09) for the second IGFBP-1 tertile and 1.47 (p=0.02) for the highest IGFBP-1 tertile, with an HR of 1.22 (95% CI=1.07–1.39, p < 0.01) per SD of IGFBP-1 level.

Insulin-like growth factor binding protein-1 (IGFBP-1) is an important regulatory molecule in the IGF system that may inhibit cell growth and survival by modulating IGF-I (14). A prior report of elevated IGFBP-1 levels in patients with heart failure (24) has now been extended by the finding that IGFBP-1 predicts risk of CHF in healthy older adults. Prior prospective data suggest that IGFBP-1 predicts future vascular endpoints, but none examined CHF in the elderly. Among diabetics with acute myocardial infarction (median age 70 years) in the Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction 2 (DIGAMI 2) trial, high IGFBP-1 predicted cardiovascular events and death (22). The Seven Countries Study identified high IGFBP-1 level as a predictor of cardiovascular mortality among 65 – 84 year old men (23). Prior data from older populations suggest an association between high IGFBP-1 and favorable levels of some metabolic factors such as obesity and lipids (32), as was also shown in our study. This may reflect inverse regulation of IGFBP-1 levels by insulin. Our results suggest the importance of adjustment for obesity and other risk factors in assessing the independent association of IGFBP-1 levels with vascular endpoints. Elevated circulating IGFBP-1 occurs in catabolic states including AIDS wasting (20), end-stage renal disease (17), cancer (16), energy deficiency during military training (18), and dietary restriction (21).

Progeric model organisms with premature aging phenotypes including sarcopenia and cell replicative senescence also have increased IGFBP-1 (with decreased IGF-I) (33, 34). Because IGFBP-1 is known to determine IGF-I bioavailability and has an inverse correlation with free IGF-I (13), this likely reflects inhibition of anabolic IGF-I effects by IGFBP-1 in these catabolic states. Mechanisms linking IGFBP-1 with vascular or cardiac structure and function are not clearly established. Studies in the rat indicate that IGFBP-1 infusion inhibits muscle protein synthesis in fast-twitch muscle, although this was not shown in the heart (35). Potential determinants of elevated circulating IGFBP-1 in persons at risk for CHF include oxidative stress (15), cytokine activity (36, 37), ephinephrine or norepinephrine (38), and subclinical liver disease or hepatic insulin resistance (39).

IGF-I, the main target for IGFBP-1, has known effects on myocardial contractility (40, 41), resistance to ischemia (42), and myocyte aging and senescence (43). However, we found no association between low total IGF-I level and CHF. Prior studies have linked changes in circulating IGF-I with onset and progression of CHF (24, 44, 45). Among patients with obstructive or non-obstructive hypertrophic cardiomyopathy, IGF-I increases prior to the onset of CHF, and then decreases below control levels after CHF onset (24). Another study observed elevated IGF-I in mild-to-moderate CHF, with decreases in IGF-I with more severe symptomatic CHF (44). The only population-based study of similar design to ours was from the Framingham Heart Study (7). We did not replicate that study's findings of increased CHF risk among older adults with low IGF-I (relative risk ~ 2 comparing below versus above the median IGF-I level, and relative risk ~ 2.5 comparing below versus above the 10^{th} percentile IGF-I level). Compared with the prior report from Framingham, the present study had important methodological differences including larger sample size (n=566 vs 56 CHF cases), availability of fasting blood specimens, and a different CHF case definition (27). The only other prospective epidemiological study in this area suggested that a CA repeat in the *IGF1* promoter region was overrepresented among CHF cases as compared with population-based controls (46), although the functional relevance of this genetic variant is unconfirmed (47) and serum IGF-I levels were unavailable.

We observed an association between hyperinsulinemia and CHF, but this association did not persist after adjustment for other risk factors. Ingelsson reported that euglycemic insulin clamp glucose disposal rate and fasting proinsulin levels were robust predictors of CHF in elderly men, although fasting insulin was a relatively weak and borderline-significant risk factor (48). We lacked direct measurements of insulin sensitivity or secretion.

Limitations include the observational design, which make it unclear whether IGFBP-1 may play a causal role in CHF. To strengthen conclusions about prospective associations, our population was limited to individuals who were free of prior cardiovascular events and we excluded underweight individuals because of the known changes in IGFBP-1 with malnutrition and wasting. Some potential confounding variables such as liver function tests were not available. Moreover, our investigation was not designed to answer the clinically important question of whether IGFBP-1 may add prognostic ability beyond other novel CHF biomarkers (e.g., BNP, ADMA). We note that the hazard ratio for IGFBP-1 in this study, while significant, suggested a weaker ability to predict CHF than what has been reported elsewhere for plasma natriuretic peptides (49). IGF-I and IGFBP levels are known to change over time, but we relied upon a single baseline measurement to characterize individuals during followup.

In summary, high IGFBP-1 is a predictor of increased risk of CHF among adults 65 years and older, after adjustment for known CHF risk factors, metabolic variables, and inflammatory biomarkers.

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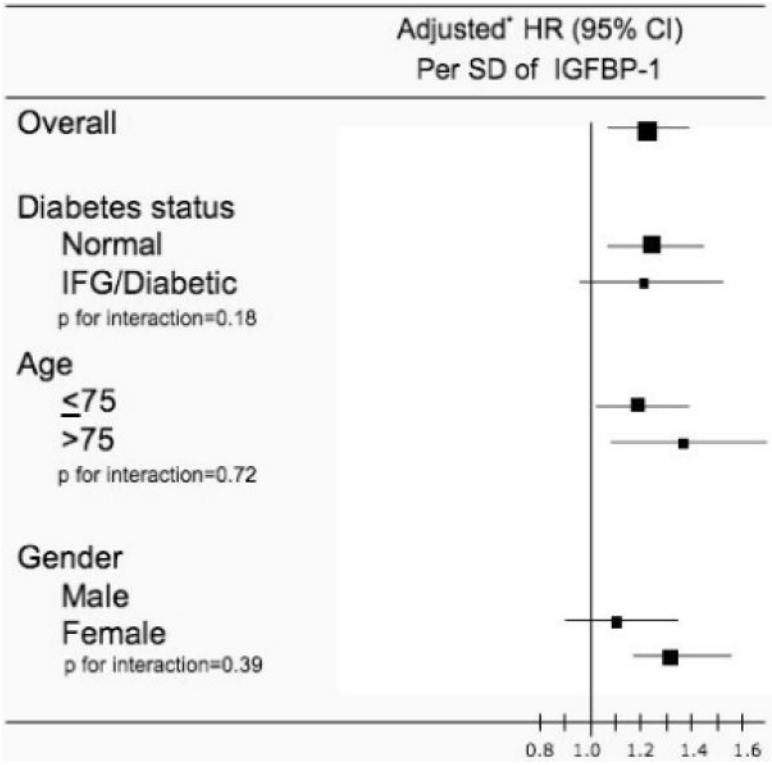

Figure.

Risk of CHF per SD of IGFBP-1 level, by subgroups defined by diabetes/IGF status, gender, and age.

Hazard ratio is indicated by boxes (with box size proportional to sample size in subgroups) and 95% confidence intervals are indicated by horizontal lines.

*Adjusted for age, race, gender, hypertension, systolic BP, HDL-c, LDL-c, total cholesterol, ECG-LVH, CAD, CRP, general health, diabetes/IFG and BMI.

Table 1

Baseline characteristics of CHF cases and comparison subjects

	CHF cases (n=566)	Comparison subjects (n=1072)
	%	
Age ≤75	55.7	69.2
>75	44.4	30.8
Male	42.4	35.7
Female	57.6	64.3
Non-Hispanic White	83.4	81.8
Other race	16.6	18.2
Excellent/v. good/good health	69.8	81.0
Poor or fair health	30.2	19.0
Income <$25,000	69.7	60.5
$25,000–$50,000	19.9	26.0
>$50,000	10.4	13.5
Smoking Former	39.1	40.0
Current	12.2	11.4
Impaired fasting glucose	15.4	13.7
Diabetes	19.1	11.3
Normal weight (BMI 18.5 – 25)	31.4	38.1
Overweight (BMI 25–30)	42.0	40.4
Obese (BMI >=30)	26.6	21.5
Treated hypertension	48.1	37.0
Angina	14.7	12.3
Alcohol use	41.7	52.5
Estrogen use	6.0	8.1
Thyroid hormone use	8.8	7.7
Oral steroid use	4.6	2.4
Diuretic use	34.8	24.8
ACE-inhibitor use	8.3	6.5
Kidney disease	3.2	1.0
Liver disease	0.6	0.5
	mean (SD)	
BMI (kg/m^2)	27.7 (5.2)	27.0 (4.9)
Total cholesterol (mg/dL)	209.4 (38.8)	214.6 (38.1)
HDL cholesterol (mg/dL)	53.0 (15.0)	55.0 (14.8)
LDL cholesterol (mg/dL)	128.6 (35.5)	132.0 (34.8)
Fasting insulin (IU/ml)	16.1 (10.8)	14.8 (11.9)
Fasting glucose (mg/dL)	115.3 (41.9)	107.4 (29.0)
C-reactive protein (mg/L)	6.1 (10.6)	4.4 (7.2)
Creatinine (mg/dL)	1.11 (0.5)	1.03 (0.4)
Albumin (g/dL)	4.0 (0.3)	4.0 (0.3)

	CHF cases (n=566)	Comparison subjects (n=1072)
IGF-I (ng/ml)*	154.2 (62.8)	153.1 (57.7)
IGFBP-1 (ng/ml)*	32.5 (20.7)	30.4 (19.2)
IGFBP-3 (ng/ml)*	4003.1 (893.5)	4053.1 (894.7)

* Comparison of CHF cases with non-cases, p=0.51 for IGF-I, p=0.04 for IGFBP-1, and p=0.10 for IGFBP-3

Table 2

Characteristics by quartile of IGFBP-1 level, among comparison subjects

	Quartiles of IGFBP-1				
	1	**2**	**3**	**4**	**p-value**
			%		
Male	38.8	41.0	36.9	26.1	<0.01
Female	61.2	59.0	63.1	73.9	
Non-Hispanic White	70.5	80.6	86.9	89.2	<0.001
Other race	29.5	19.4	13.1	10.8	
Exc/V.Good/Good health	76.4	79.4	86.5	81.7	0.02
Poor/Fair health	23.6	20.6	13.5	18.3	
Former smoker	44.0	42.2	37.7	36.2	0.67
Current smoker	8.6	11.6	10.8	14.6	
Impaired fasting glucose	18.7	14.6	15.7	5.6	<0.001
Diabetes	14.6	13.1	4.5	13.1	
Treated hypertension	42.5	35.1	35.1	35.4	0.20
Angina	11.2	11.2	12.7	14.2	0.68
Estrogen use	1.5	4.9	7.8	18.3	<0.01
Thyroid hormone use	8.2	6.7	4.5	6.7	0.37
Oral steroid use	7.1	4.9	10.1	9.0	0.12
Diuretic use	26.9	23.1	23.5	25.8	0.71
ACE-inhibitor use	4.5	1.9	1.9	1.5	0.09
Kidney disease	0.8	0.0	0.4	0.8	0.53
Liver disease	0.8	0.8	1.2	1.2	0.94
			Mean (SD)		
Age (years)	71.1 (4.5)	72.0 (4.9)	72.5 (5.4)	73.8 (6.2)	<0.001
BMI (kg/m^2)	30.1 (5.7)	27.4 (4.1)	25.9 (3.8)	24.8 (4.1)	<0.001
Total cholesterol (mg/dL)	214.2 (35.2)	219.1 (38.2)	213.0 (38.2)	212.3 (40.4)	0.15
HDL cholesterol (mg/dL)	50.4 (12.4)	54.1 (13.2)	56.0 (15.1)	59.5 (16.8)	<0.001
LDL cholesterol (mg/dL)	132.8 (31.0)	136.4 (34.7)	132.1 (34.7)	127.0 (38.0)	0.02
Fasting glucose (mg/dL)	110.4 (24.6)	109.4 (27.9)	102.6 (22.6)	107.2 (37.9)	<0.001

	Quartiles of IGFBP-1				
	1	2	3	4	p-value
Fasting insulin (IU/ml)	19.6 (10.5)	16.2 (18.7)	12.3 (5.8)	11.2 (5.1)	<0.001
C-reactive protein (mg/L)	4.9 (8.5)	4.1 (5.9)	4.4 (7.1)	4.3 (7.1)	0.02
IGF-I (ng/ml)	168.6 (54.3)	163.5 (57.6)	145.9 (51.1)	134.5 (61.3)	<0.001
IGFBP-3 (ng/ml)	4205.7 (982.1)	4142.0 (900.0)	3968.9 (820.6)	3895.9 (836.4)	<0.001