Insulin-like growth factor-(IGF)-axis, inflammation, and glucose intolerance among older adults

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Abstract

Increasing evidence suggests that the insulin-like growth factor (IGF)-axis may play a role in glucose metabolism and may also be associated with systemic inflammation. The aim of this study was to evaluate the association of insulin-like growth factor-1 (IGF-I) and its binding proteins, IGFBP-1 and IGFBP-3, with glucose intolerance and inflammation among older adults. We conducted a cross-sectional analysis in a in a random subsample ($n = 922$) of the Cardiovascular Health Study (CHS), a prospective cohort of men and women $\geqslant 65$ years. Mean IGFBP-1 levels were significantly lower in older adults with impaired glucose tolerance (IGT), impaired fasting glucose (IFG) and diabetes compared to those with normal fasting and post-load glucose. High IGFBP-1 was associated with a reduced prevalence of IGT and IFG; the multivariable OR between extreme quartiles of IGFBP-1 was 0.60 (95% CI: 0.37, 0.95; p-trend: 0.03) for IGT and 0.41 (95% CI: 0.26, 0.64; p-trend: <0.01) for IFG. We did not find any significant association between IGF-I and glucose intolerance in this study and the association for IGFBP-3 was less clear. However, low levels of IGF-I and IGFBP-3 were associated with increased levels of markers of inflammation including C-reactive protein and interleukin-6 levels. We conclude that among adults $\geqslant 65$ years, low IGFBP-1 levels are associated with increased prevalence of glucose intolerance. We did not confirm prior associations of low IGF-I with glucose intolerance in this cohort of older individuals.

Keywords: IGF-I; IGFBP-I; Inflammation; Glucose intolerance

1. Introduction

Insulin-like growth factor (IGF)-1 is the primary mediator of the effects of growth hormone and shares structural homology with insulin. Increasing evidence

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suggests a role of the IGF-axis in the maintenance of normal glucose homeostasis [1] and inflammation [2]. In circulation, most IGF-I is bound to specific high-affinity binding proteins (IGFBP-1 to IGFBP-6) mainly produced in the liver [3]. These proteins not only modulate IGF-I bioactivity but may also have independent metabolic effects [4]. IGFBP-3 is the most abundant of all IGFBPs and binds more than 90–95% of the IGF-I in serum. IGFBP-1 is a 28 kDa protein and its levels in circulation are tightly regulated by insulin and have a strong inverse correlation with fasting insulin levels [5]; however, its specific role is not completely understood. It is suggested that IGFBP-1 is the only binding protein involved in acute regulation of IGF-I bioavailability [5] and may play a role to prevent hypoglycemia [6]. In contrast to the increased hepatic production of IGFBP-1 at low insulin levels, there is a dynamic suppression of IGFBP-1 synthesis in presence of peripheral insulin resistance [7].

Both animal and human data demonstrate that IGF-I gene mutation results in a state of insulin resistance that improves with IGF-I therapy [8,9]. In addition, among older adults a polymorphism in the promoter region of the IGF-I gene was associated with low IGF-I levels and a 70% elevated risk of type 2 diabetes [10]. In a British study among adults aged 45–65 years (n = 615) [11], a low total IGF-I was associated with increased risk of impaired glucose tolerance (IGT) and diabetes. Further, the authors reported that an inverse association of total IGF-I and subsequent 2-h glucose concentrations was seen only among people with low IGFBP-1. Because aging is associated with changes in the IGF-axis including a decrease in IGF-I and an increase in IGFBP-1 levels [12–14], it is uncertain whether similar associations exist among older adults. To evaluate this association in the elderly, we conducted the current study within the Cardiovascular Health Study (CHS), a prospective cohort of men and women aged ⩾65 years. In addition, we also evaluated the association between inflammatory markers and IGF-axis based on recent epidemiological data indicating anti-inflammatory effects of IGF-I [15].

2. Material and methods

The CHS is a population-based, prospective cohort study of risk factors for cardiovascular and cerebrovascular disease in older people [16]. In 1989/1990, 5201 community-dwelling elderly adults aged ⩾65 years were recruited from four U.S. communities (Washington County, MD; Allegheny County, PA; Forsyth County, NC; and Sacramento County, CA) based on a randomly generated sampling frame derived from the Health Care Financing Administration. Participants provided informed consent according to the guidelines created by the institutional review boards at each clinic site. At baseline data on anthropometric measures, demo-graphics, lifestyle factors and medical history were collected. An oral glucose tolerance test (OGTT) with 75-g glucose was performed at baseline in the original CHS cohort of 5021 and at year 7 among all participants without known diabetes. In 1992/1993, 687 African-American adults aged ⩾65 years were added to the original cohort; however this second cohort was not included in this study due to lack of data on OGTT in this group. CHS participants completed standardized clinical examinations and questionnaires at study baseline and at nine annual follow-up visits [16].

The current study was conducted within a random sample of the original cohort without prevalent cardiovascular disease (CVD) at baseline (n = 978) selected as part of a case-cohort study evaluating the association between IGFs and incident CVD. We conducted a cross-sectional analysis among 922 participants after excluding people without OGTT data (n = 31) and diabetic individuals treated with insulin (n = 25). In addition, a prospective analysis was conducted separately among 301 participants with normal glucose tolerance (NGT; 2-h post-load glucose of <140 mg/dl) and 254 participants with normal fasting glucose levels (<100 mg/dl) at baseline.

2.1. Diagnosis of glucose intolerance

Participants were considered to have diabetes if they reported pharmacological treatment for hyperglycemia (insulin or oral agents) at baseline or during follow-up based on annual medical questionnaires. In addition, to diagnose glucose intolerance (which includes IGT, impaired fasting glucose [IFG] and diabetes), we used two criteria; one based on OGTT and the other based on overnight (12–16 h) fasting glucose [17]. According to the World Health Organization based primarily on OGTT [18], diabetes was defined as a 2-h postload glucose ⩾200 mg/dl or fasting glucose ⩾140 mg/dl, IGT as a 2-h postload glucose 140–199 mg/dl and fasting glucose <140 mg/dl, and NGT as a 2-h postload glucose <140 mg/dl. Based on the American Diabetes Association [19], diabetes was defined as a glucose ⩾126 mg/dl, IFG was defined as glucose between 100 and 125 mg/dl, and normal fasting (NFG) as a glucose <100 mg/dl.

2.2. Laboratory measurements

Details of all laboratory procedures in the CHS have been previously reported [20]. In this study, total IGF-I, IGFBP-1, and IGFBP-3 were measured using enzyme-linked immunosorbent assay methods (Diagnostics Systems Laboratory, Webster, TX) in fasting blood samples. The within- 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. Plasma glucose was measured with a Kodak Ektachem

700 Analyzer (Eastman Kodak Corp., Rochester, NY) and insulin was measured by a competitive RIA (Diagnostic Products Corp., Malvern, PA).

2.3. Statistical analysis

All statistical analyses were performed with SAS® software (SAS Institute Inc., Cary, NC). Descriptive analysis of the baseline data included calculating means for continuous variables and proportions for categorical variables. To evaluate the correlation between IGFs, anthropometric factors (height, weight, body mass index [BMI], waist circumference), fasting and 2-h postload glucose and insulin, homeostasis model assessment for insulin resistance (HOMA-IR), and inflammatory factors (C-reactive protein [CRP], fibrinogen, Factor VII, Factor VIII, interleukin-6 [IL-6], albumin, and fibrinogen), we estimated the partial spearman coefficients adjusted for age, race and gender. In all analyses presented, we excluded individuals who were on insulin therapy ($n = 25$); however, in secondary analyses we included these individuals and the results were similar. For all analyses, we modeled the main exposure variables in quartiles since this method does not make a linearity assumption and is not impacted by outliers. To examine the association between the quartiles of IGFs and glucose intolerance, we used unconditional multivariable logistic regression analysis. We estimated the odds ratio (OR) and the 95% confidence intervals (CI) with the lowest quartile as the reference group. In the multivariable models, we considered following covariates: age (10-year categories), gender, race and smoking. Further, since obesity is a well-established risk factor for diabetes and a strong correlate of IGFBP-1 levels, we added BMI to the models to see its impact on the effect estimates. Further inclusion of waist circumference in the model in addition to BMI did not change the results. We also evaluated the inclusion of CRP in the models as well as effect modification by CRP and BMI. Tests of linear trend across quartiles of IGFs were conducted by assigning median value for each quartile and fitting this continuous variable in the model. All p-values were two-tailed and p-values below 0.05 were considered statistically significant.

3. Results

3.1. Subject characteristics

Compared to participants with NGT ($n = 470$, 33.3 ng/ml), those with abnormal glucose tolerance at

Table 1
Cross-sectional evaluation of risk factors for impaired glucose tolerance (IGT) and diabetes at baseline

Categorical variables	% (n)	OR (95% CI)	OR (95% CI)
		IGT ($n = 294$) vs. NGT ($n = 470$)	Diabetes ($n = 158$) vs. NGT ($n = 470$)
Age			
<70	37.7 (348)	1.0	1.0
70 − 80	52.0 (479)	1.10 (0.80, 1.50)	1.25 (0.84, 1.86)
80 +	10.3 (95)	0.87 (0.50, 1.51)	1.75 (0.97, 3.16)
Gender			
Male	34.9 (322)	1.0	1.0
Female	65.1 (600)	1.32 (0.97, 1.80)	1.23 (0.84, 1.81)
Race			
White (non-Hispanic)	93.8 (865)	1.0	1.0
Other	6.2 (57)	1.31 (0.71, 2.42)	1.45 (0.71, 2.97)
Smoking status			
Never	48.7 (449)	1.0	1.0
Former	40.5 (373)	0.81 (0.59, 1.13)	0.84 (0.56, 1.23)
Current	10.9 (100)	0.58 (0.35, 0.98)	0.89 (0.49, 1.62)
Continuous variables	Mean ± SD	OR (95% CI)	OR (95% CI)
Body mass index (kg/m^2)	26.5 ± 4.7	1.28 (1.10, 1.50)	1.78 (1.47, 2.16)
Waist circumference (cm)	93.1 ± 13.2	1.33 (1.14, 1.55)	1.74 (1.43, 2.12)
Fasting insulin (IU/ml)	14.8 ± 12.3	1.45 (1.10, 1.92)	3.89 (2.77, 5.47)
C-reactive protein (mg/l)	4.1 ± 7.2	1.05 (0.87, 1.27)	1.31 (1.10, 1.57)
IGF-I (ng/ml)	152.6 ± 56.3	1.03 (0.89, 1.20)	1.14 (0.95, 1.36)
IGFBP-1 (ng/ml)	32.1 ± 19.7	0.73 (0.62, 0.86)	0.68 (0.55, 0.84)
IGFBP-3 (ng/ml)	4,129.3 ± 865.4	1.13 (0.97, 1.32)	1.19 (0.98, 1.44)

OR, odds ratio; CI, confidence interval; HOMA-IR, homeostasis model assessment of insulin resistance; OGTT, oral glucose tolerance test; NGT, normal glucose tolerance.

All ORs are adjusted for age (in 10-year categories), gender and race/ethnicity. For continuous variables, the ORs are estimated for one standard deviation increase.

baseline had significantly lower IGFBP-1 levels (IGT: $n = 294$; 28.0 ng/ml; $p < 0.001$; diabetes: $n = 158$; 26.8 ng/ml; $p < 0.001$). In addition, compared to individuals with NFG ($n = 449$), IGFBP-1 levels were lower among those with IFG ($n = 381$); 36.4 ng/ml vs. 27.6 ng/ml; $p < 0.001$. Table 1 shows the ORs for prevalent IGT or diabetes in relation to IGF variables and other risk factors at baseline. As expected, abnormal glucose tolerance was significantly associated with higher BMI, waist circumference, fasting insulin, and CRP levels. In addition, prevalent IGT and diabetes were inversely associated with IGFBP-1 levels (IGT: OR for one standard deviation [SD] increase: 0.73, 95% CI: 0.62, 0.86; diabetes: OR for one SD increase: 0.68; 95% CI: 0.55, 0.84).

3.2. Correlations with IGFs

IGFBP-1 levels were correlated more strongly with anthropometric factors and measures of glucose tolerance than were IGFBP-3 and IGF-I (Table 2). Adjusted for age, gender, and race, spearman rank correlations between IGFBP-1 and weight, BMI, waist circumference, and HOMA-IR were in the range of $r = -0.3$ to $r = -0.5$. IGF-I and IGFBP-3 positively correlated with

albumin and negatively correlated with CRP and IL-6, especially among NGT individuals. IGFBP-1 and albumin levels had an inverse correlation among NGT and diabetic individuals. Further, IGFBP-1 correlated inversely with triglycerides and LDL and positively with HDL and these correlations were in the opposite direction for IGFBP-3.

3.3. IGFs and glucose intolerance

Table 3 shows the ORs and 95% CI for abnormal glucose tolerance using the OGTT and fasting glucose criteria separately. In a logistic regression model, adjusted for age, gender, race and smoking, the OR for prevalent IGT comparing extreme quartiles of IGFBP-1 was 0.50 (95% CI: 0.32, 0.77; p for trend: 0.001). This association was slightly attenuated when BMI was added to the model (OR: 0.60; 95% CI: 0.37, 0.95; p for trend: 0.03). The results were slightly stronger when we used the fasting glucose criteria; for prevalent IFG, OR between extreme quartiles of IGFBP-1 was 0.41 (95% CI: 0.26, 0.64; p for trend: <0.0001) in the multivariable model that included BMI. The multivariate OR between extreme quartiles for prevalent diabetes

Table 2
Partial spearman correlations, adjusted for age, gender and race, between IGFs, anthropometric variables, metabolic and inflammatory factors

	Normal ($n = 470$)			Impaired glucose tolerance ($n = 294$)			Diabetes ($n = 158$)		
	IGF-I	IGFBP-1	IGFBP-3	IGF-I	IGFBP-1	IGFBP-3	IGF-I	IGFBP-1	IGFBP-3
Anthropometric variables									
Height	0.04	−0.09	0.07	0.02	−0.17[b]	−0.03	−0.02	−0.11	0.00
Weight	−0.05	−0.40[d]	−0.01	0.07	−0.54[d]	0.13[a]	−0.05	−0.39[d]	0.04
Body mass index	−0.06	−0.41[d]	−0.03	0.05	−0.49[d]	0.16[b]	−0.04	−0.33[d]	0.04
Waist circumference	−0.08	−0.40[d]	−0.05	0.04	−0.47[d]	0.13[a]	0.05	−0.29[c]	0.07
Metabolic factors									
Fasting glucose	0.17[c]	−0.29[d]	0.18[d]	0.09	−0.22[c]	0.09	−0.06	0.07	−0.04
2-h glucose	0.05	−0.21[d]	0.07	0.03	−0.09	−0.03	−0.02	−0.04	0.07
Fasting insulin	0.03	−0.47[d]	0.03	0.10	−0.49[d]	0.05	−0.01	−0.43[d]	−0.08
2-h insulin	0.11[a]	−0.40[d]	0.10[a]	0.03	−0.35[d]	0.09	0.20[a]	−0.32[c]	0.15
HOMA-IR	0.06	−0.48[d]	0.06	0.11	−0.50[d]	0.06	−0.05	−0.26[b]	−0.09
Inflammatory markers									
C-reactive protein	−0.22[d]	−0.08	−0.16[c]	−0.13[a]	−0.10	−0.10	−0.08	0.17[a]	0.06
Factor VII	−0.01	−.05	0.11[a]	0.07	−0.04	0.17[b]	0.13	0.01	0.29[c]
Factor VIII	−0.04	0.08	0.01	0.03	0.03	0.05	−0.09	0.11	−0.11
Interleukin-6	−0.16[c]	−0.08	−0.11[a]	−0.09	−0.01	−0.08	−0.16	0.01	−0.16
Albumin	0.11[b]	−0.20[d]	0.15[c]	0.05	−0.09	0.06	0.00	−0.18[a]	0.05
Fibrinogen	0.05	−0.05	0.02	0.06	−0.07	0.07	0.18	0.09	0.12
Vascular risk factors									
Triglycerides	0.06	−0.12[b]	0.14[b]	0.02	−0.27[d]	0.20[c]	−0.02	−0.15	0.16[a]
LDL	0.08	−0.13[b]	0.13[b]	0.14[a]	−0.05	0.23[d]	0.07	−0.02	0.22[b]
HDL	−0.09	0.23[d]	−0.04	−0.02	0.22[c]	−0.07	−0.04	0.05	0.00
SBP	−0.09[a]	−0.08	−0.08	−0.10	−0.02	−0.08	0.00	−0.06	0.07
DBP	−0.03	−0.06	−0.01	−0.11	−0.11	−0.07	0.07	−0.15	0.07
Creatinine	0.05	0.09	−0.01	0.05	0.04	0.03	−0.01	0.09	0.06

HOMA-IR, homeostasis model assessment of insulin resistance.
[a] $p \leqslant 0.05$.
[b] $p \leqslant 0.01$.
[c] $p \leqslant 0.001$.
[d] $p \leqslant 0.0001$.

Table 3
Odds ratios (95% confidence intervals) for the prevalence of impaired glucose tolerance, impaired fasting glucose and diabetes at baseline by quartiles of IGFBP-1

	Quartiles of IGFBP-1[a]				p-Trend
	Q_1	Q_2	Q_3	Q_4	
OGTT criteria					
IGT ($n = 294$) vs. NGT ($n = 470$)					
Number of cases	106	71	61	56	
OR (95% CI) adjusted for age, gender, race, and smoking	1 (reference)	0.68 (0.46, 1.01)	0.55 (0.36, 0.83)	0.50 (0.32, 0.77)	0.001
OR (95% CI) adjusted for age, gender, race, smoking and BMI	1 (reference)	0.74 (0.49, 1.12)	0.64 (0.41, 0.99)	0.60 (0.37, 0.95)	0.03
Diabetes ($n = 158$) vs. NGT ($n = 470$)					
Number of cases	56	45	32	25	
OR (95% CI) adjusted for age, gender, race, and smoking	1 (reference)	0.78 (0.49, 1.26)	0.53 (0.32, 0.89)	0.38 (0.22, 0.66)	0.0003
OR (95% CI) adjusted for age, gender, race, smoking and BMI	1 (reference)	1.02 (0.62, 1.67)	0.78 (0.45, 1.35)	0.60 (0.33, 1.10)	0.07
Fasting glucose criteria					
IFG ($n = 381$) vs. NFG ($n = 449$)					
Number of cases	151	104	69	57	
OR (95% CI) adjusted for age, gender, race, and smoking	1 (reference)	0.62 (0.42, 0.90)	0.35 (0.23, 0.52)	0.28 (0.19, 0.43)	<0.0001
OR (95% CI) adjusted for age, gender, race, smoking and BMI	1 (reference)	0.73 (0.49, 1.07)	0.47 (0.31, 0.72)	0.41 (0.26, 0.64)	<0.0001
Diabetes ($n = 92$) vs. NFG ($n = 449$)					
Number of cases	32	24	18	18	
OR (95% CI) adjusted for age, gender, race, and smoking	1 (reference)	0.69 (0.38, 1.27)	0.44 (0.23, 0.84)	0.44 (0.22, 0.87)	0.01
OR (95% CI) adjusted for age, gender, race, smoking and BMI	1 (reference)	1.01 (0.53, 1.94)	0.89 (0.43, 1.84)	0.97 (0.45, 2.05)	0.88

OGTT, oral glucose tolerance test; IGT, impaired glucose tolerance; IFG, impaired fasting glucose; NFG, normal fasting glucose; NGT, normal glucose tolerance; BMI, body mass index.

[a] Cutpoints for quartiles of IGFBP-1 are based on 470 normal glucose tolerant persons; Q_1 (>19.7 ng/ml), Q_2 (19.8-30.6 ng/ml), Q_3 (30.7-46.8 ng/ml), Q_4 (>46.8 ng/ml).

was 0.38 (95% CI: 0.22, 0.66; p for trend: 0.0003) which remained marginally significant when BMI was added to the model (OR: 0.60; 95% CI: 0.33, 1.10; p for trend: 0.07). However, with the fasting glucose criteria, this OR for prevalent diabetes was not statistically significant.

Among 301 NGT individuals who had fasting glucose measured at year 7, high IGFBP-1 levels had a border-line significant reduced risk of developing IFG/diabetes. Adjusted for age, gender, race, smoking and BMI, ORs for incident IFG/diabetes were 0.78 (95% CI: 0.37, 1.66) for IGFBP-1 quartile 2, 0.60 (95% CI: 0.26, 1.38) for IGFBP-1 quartile 3, and 0.43 (95% CI: 0.16, 1.17) for IGFBP-1 quartile 4, compared with the first IGFBP-1 quartile (p for trend: 0.08; $n = 63$ subjects with IFG/diabetes at year 7). In an analysis using the OGTT criteria, there was no significant association between IGFBP-1 levels and the risk of incident IGT/diabetes; the multivariate OR between extreme IGFBP-1 quartiles was 0.67 (95% CI: 0.25, 1.79; p for trend: 0.47; $n = 254$ of which 60 individuals developed IGT/diabetes at year 7).

We found that high IGF-I and IGFBP-3 levels were associated with glucose intolerance in some multivariate models in both cross-sectional and prospective analyses. However, in general, these associations were not monotonically linear or lost significance after controlling for IGFBP-1. On the other hand, associations of IGFBP-1 remained significant even after accounting for IGF-I and IGFBP-3 levels.

3.4. Additional analyses

In both cross-sectional and prospective analyses relating IGFBP-1 with glucose intolerance, further adjustment for CRP did not impact our results. In stratified analyses and multivariate models that included interaction terms, we did not find effect modification for the IGFBP-1 associations by IGF-I, IGFBP-3, BMI or CRP. When we modeled the molar ratio of IGF-I: IGFBP-1, a surrogate for IGF-bioavailability, the significant associations for this ratio appeared to be entirely attributable to IGFBP-1.

4. Discussion

In this study among adults 65 years and older, we found that individuals with glucose intolerance had lower IGFBP-1 levels compared to those with normal glucose tolerance. IGFBP-1 levels also correlated inversely with measures of adiposity and insulin resistance. We did not find any significant association between IGF-I and glucose intolerance in this study and the association for IGFBP-3 was less clear.

As expected, we found a negative correlation between IGFBP-1 and insulin levels. Our finding of an inverse correlation between IGFBP-1 and adiposity is consistent with several previous investigations [21–24]. Increased adiposity is commonly associated with peripheral hyperinsulinemia which may impact IGFBP-1 levels due to the inhibitory effect of insulin on hepatic synthesis and release of IGFBP-1. [5,25]. Some data suggest that the regulation of IGFBP-1 by insulin may decrease with age [14] and in type 2 diabetes [21,26,27]. However, we observed a strong inverse correlation of IGFBP-1 with insulin among diabetic members of this elderly cohort.

Aging-induced changes in the growth hormone/IGF-axis have been well described, with IGF-I and IGFBP-3 decreasing and IGFBP-1 increasing with age [12–14,28]. However, it remains unclear if these changes are associated with risk of age-associated medical conditions. The present data suggest that IGFBP-1 levels, but not total IGF-I levels, are associated with glucose intolerance in the elderly. Previously, Sandhu et al [11], in a prospective design with 4.5 years of follow-up, reported that high IGF-I levels were associated with a reduced risk of developing IGT or diabetes in people aged 45–65 years. The OR comparing people with IGF-I levels $\geqslant$ median (19.8 nmol/l) to people with levels less than median was 0.50 (95% CI: 0.26, 0.95). Further, they reported that an inverse association of total IGF-I and subsequent 2-h postload glucose concentrations was only seen in participants with IGFBP-1 concentrations $\leqslant$ median (5.5 nmol/l). Other studies among younger populations are also consistent with our findings suggesting an association between low IGFBP-1 and abnormal glucose tolerance. In a prospective study evaluating risk factors for gestational diabetes (GDM), investigators reported a 57% reduced risk for GDM among women in the highest tertile of IGFBP-1 [29]. The relative risk for developing GDM, comparing women with IGFBP-1 $\geqslant$ 15.1 nmol/l to those with IGFBP-1 $<$ 7.9 nmol/l, was 0.43 (95% CI: 0.18, 1.05; p for trend: 0.059). In another study, family history of type 2 diabetes in adolescents was associated with lower levels of IGFBP-1 (9.5 vs. 3.7 nmol/l; p-value: 0.002), although this was not observed with total IGF-I levels [30].

In this study, we did not find any significant association between total IGF-I level and glucose intolerance. Thus, the association of low IGF-I with glucose intoler-ance previously reported among middle-aged persons [11] may not hold among older adults, possibly because this association is masked by other age-related co-morbidities or changes in metabolism that lead to reduced circulating IGF-I levels. Similarly, in a prior report from our cohort, we found that low IGF-I predicted non-fatal myocardial infarction, but not fatal coronary events or ischemic stroke. [31], which was somewhat inconsistent with prior data from middle-aged populations linking low IGF-I with increased risk of incident ischemic heart disease [32] and stroke [33]. One limitation of our investigation is that we did not measure 'free' IGF-I levels, the unbound or readily dissociable fraction of IGF-I, which is strongly correlated with IGFBP-1 levels [34]. In the previously mentioned study evaluating the association of IGFs and GDM, high levels of free IGF-I were associated with a significantly reduced risk of GDM while total IGF-I levels were not [29]. Changes in IGFBP-1 levels may impact the bioavailability of free IGF-I and modify its effects [35]. In our study, high IGFBP-1 levels, which may indicate a reduced IGF-I bioavailability, were associated with lower risk of glucose tolerance. IGF-I has insulin-like metabolic effects and high IGF-I levels have been linked with increased insulin sensitivity and improved glucose tolerance [11,36]. Therefore, these data suggest that the association between IGFBP-1 and glucose intolerance may not be explained by insulin-like effects of IGF-I in the elderly. Low IGFBP-1 may also be a marker of increased infiltration of fat in the liver [37], which is another potential explanation for the observed link with glucose intolerance.

A potential mechanism by which the IGF-axis system may affect glucose tolerance is through its potential interaction with inflammatory mechanisms. We found that low IGF-I and IGFBP-3 levels were associated with systemic markers of inflammation including high CRP and IL-6 and low albumin, although not with glucose tolerance. *In vitro* data suggest that IGFBP-1 synthesis is upregulated by pro-inflammatory cytokines including tumor necrosis factor-alpha (TNF-α), interleukin-(IL)-1 and IL-6 [38–41]. In this study, IGFBP-1 was correlated with inflammatory markers (high CRP and low albumin) among the subset of our population with diabetes, but this association was less consistent among non-diabetic individuals. Moreover, the association between IGFBP-1 levels and glucose intolerance was not affected by adjustment or stratification for CRP.

Our study has a few limitations. The prospective analysis was restricted by the small sample size and use of a single follow-up measure of glucose tolerance at year 7. In this study, we also used a single measure of each IGF variable; however, single measurements are prone to random errors which in general bias the results towards the null. Since obesity is a strong risk factor for diabetes, residual confounding by adiposity

of the association between IGFBP-1 and glucose intolerance is a potential concern. In our study, when we controlled for adiposity using BMI and waist circumference in the same multivariable models, the results were similar. Due to the observational nature of this study, we are unable to exclude the possibility that IGFBP-1 may just be a marker of the insulin resistance and may not have any direct role in the etiology of glucose intolerance or diabetes.

In summary, the results of this study suggest that low IGFBP-1 levels, but not total IGF-I levels, are associated with glucose intolerance in the elderly. Future research including larger prospective studies is required to confirm these findings.

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